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British Journal of Anaesthesia

International Journal of Anaesthesia

Volume 87 Number 3 September 2001

Editor-in-chief: Jennifer M. Hunter

- Perioperative stress response in children
- Erythropoietin and autologous blood donation
- Tetanus

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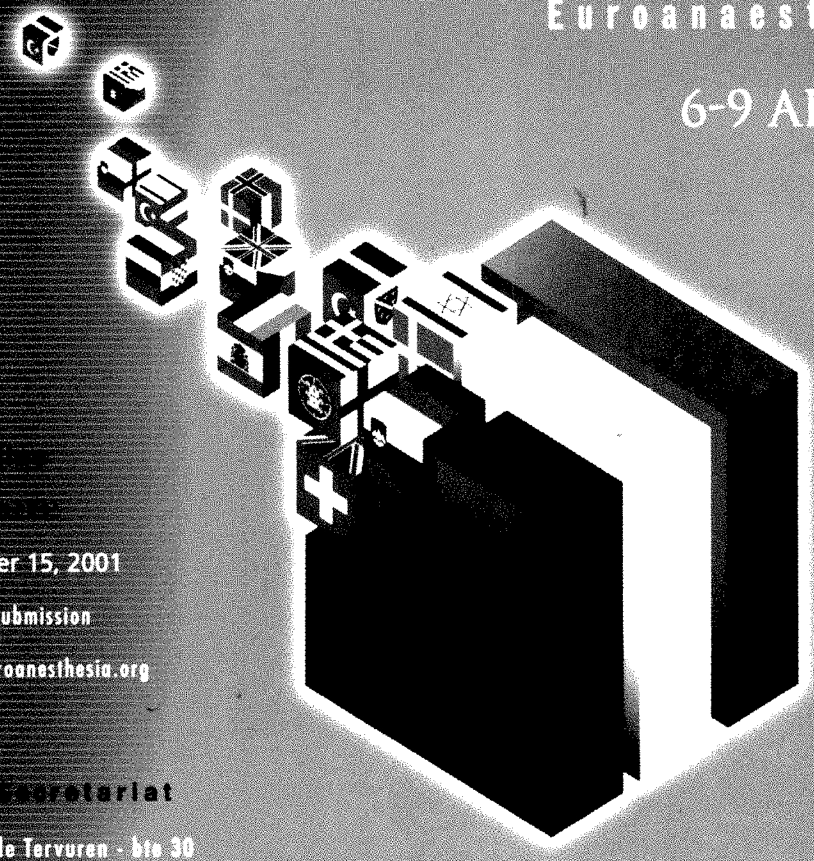

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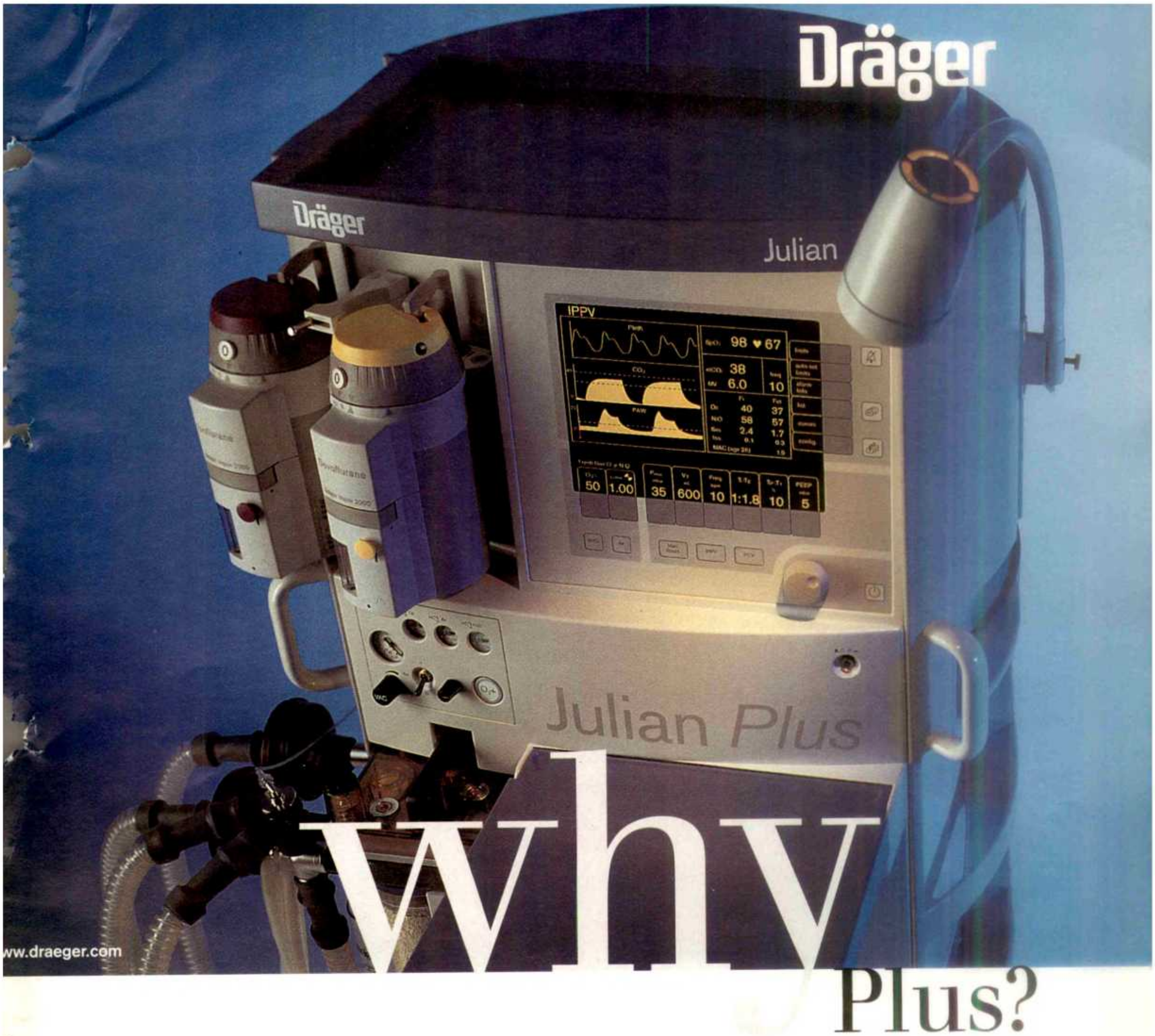

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VIOXX Tablets: 12.5 mg and 25 mg tablets each containing 12.5 mg or 25 mg of rofecoxib. VIOXX Oral Suspension: 12.5 mg/5 ml and 25 mg/5 ml, each 5 ml oral suspension containing either 12.5 mg or 25 mg of rofecoxib.

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Symptomatic relief in the treatment of osteoarthritis.

DOSAGE AND ADMINISTRATION

The adult starting dose is 12.5 mg once-daily orally with or without food. Some patients may receive additional benefit by increasing the dose to 25 mg once-daily. 25 mg daily should not be exceeded. *Elderly:* Exercise care when increasing the dose from 12.5 mg to 25 mg. *Hepatic insufficiency:* In mild hepatic insufficiency, do not exceed 12.5 mg once-daily. *Children:* Not recommended.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Moderate or severe hepatic dysfunction (Child-Pugh score ≥7). Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs.
Third trimester of pregnancy and lactation. Inflammatory bow
Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with
significantly impaired renal function, uncompensated h
or cirrhosis. Use caution when initiating treatment in p
considerable dehydration. Rehydrate patients prior
therapy with rofecoxib. Consider the possibility of fluid
exercise caution when rofecoxib is used in patients with
oedema, a history of heart failure, left ventricular dy
hypertension. Maintain appropriate supervision when
elderly or patients with renal, hepatic or cardiac dysf
rofecoxib. In clinical studies, some osteoarthritis (OA) pa
with rofecoxib developed perforations, ulcers or blee
Patients with a prior history of a PUB and patients gr
years of age appeared to be at a higher risk for a PUB
higher than 25 mg, the risks of gastro-intestinal symp
or hypertension are increased. Elevations of ALT an
times the upper limit of normal) have been reported in
1% of patients in clinical trials with rofecoxib. Any
symptoms and/or signs suggesting liver dysfunction, o
abnormal liver function test has occurred, should be
persistently abnormal liver function tests. If persistently
function tests (three times the upper limit of normal
discontinue rofecoxib. Rofecoxib may mask fever. U
is not recommended in women attempting to conceive

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Rarely, patients may develop perforations, ulcers and bleeds with VIOXX, but the risk is lower in patients treated with VIOXX than in patients treated with conventional NSAIDs.

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dynamic): Warfarin: closely monitor the prothrombin time therapy with rofecoxib is initiated or changed in patients arfarin or similar agents, particularly in the first few days. *tors:* administration of 25 mg daily of rofecoxib with 10 mg to 40 mg daily for four weeks to patients with on was associated with a small attenuation of the nsive effect compared to the ACE inhibitor alone. This onsidered in patients taking rofecoxib concomitantly with tors. *Beta-blockers and diuretics:* concomitant use of ay reduce the antihypertensive efficacy of beta-blockers s and the other effects of diuretics. *Aspirin:* at steady state, mg once-daily had no effect on the anti-platelet activity e (81 mg once-daily) aspirin. Avoid concomitant ion of rofecoxib with higher doses of aspirin or other *yclosporin/tacrolimus:* monitor renal function when d either cyclosporin or tacrolimus is used in combination. *(pharmacokinetic): Lithium:* NSAIDS may increase m concentrations. *Methotrexate:* consider adequate or methotrexate-related toxicity when rofecoxib and are administered concomitantly. *CYP1A2 substrates.* with concomitant administration of rofecoxib with drugs tabolised by CYP1A2 (e.g. theophylline, amitriptyline, leuton). *Midazolam:* a modest 30% reduction of the AUC n was seen with rofecoxib 25 mg daily, most likely due first pass metabolism through induction of intestinal vity by rofecoxib. *CYP3A4 substrates:* in spite of a on of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25-mg dose when rofecoxib is used with potent inducers of hepatic metabolism. Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1. *Pregnancy:* Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus. *Lactation:* contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months, or in post-marketing experience.

[Common (≥1/100, <1/10); Uncommon (≥1/1000, <1/100); Rare (≥1/10,000, <1/1000); Very rare (<1/10,000) and isolated cases]

Body as a whole/site unspecified: *Common:* oedema/fluid retention, abdominal pain, dizziness. *Uncommon:* asthenia/fatigue, abdominal distension, chest pain. *Very rare:* hypersensitivity reactions, including angioedema, urticaria and anaphylactic/anaphylactoid reactions. ***Blood and the lymphatic system disorders:*** *Common:* haematocrit decreased. *Uncommon:* haemoglobin decreased, erythrocytes decreased, leukocytes decreased. *Very rare:* thrombocytopenia. ***Cardiovascular system:*** *Common:* hypertension. *Very rare:* congestive heart failure. ***Digestive system:*** *Common:* heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia. *Uncommon:* constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux. *Rare:* peptic ulcers, gastro-intestinal perforation and bleeding (mainly in elderly patients), gastritis. ***Hepatobiliary disorders:*** *Common:* alanine aminotransferase increased, aspartate aminotransferase increased. *Uncommon:* alkaline phosphatase increased. *Isolated cases:* hepatotoxicity including hepatitis. ***Eyes, ears, nose and throat:*** *Uncommon:* tinnitus. *Very rare:* blurred vision. ***Metabolism and nutrition:*** *Uncommon:* weight gain. ***Musculoskeletal:*** *Uncommon:* muscular cramp. ***Nervous system:*** *Common:* headache. *Uncommon:* insomnia, somnolence, vertigo. *Very rare:* paraesthesia. *Isolated cases:* aseptic meningitis. ***Psychiatric disorder:*** *Uncommon:* depression, mental acuity decreased. *Very rare:* confusion, hallucinations. ***Respiratory system:*** *Uncommon:* dyspnoea. *Very rare:* bronchospasm. ***Urogenital:*** *Uncommon:* BUN increased, serum creatinine increased, proteinuria. *Very rare:* renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy. ***Skin and skin appendages:*** *Common:* pruritus. *Uncommon:* rash, atopic dermatitis. *Isolated cases:* cutaneo-mucosal adverse effects and severe skin reactions including Stevens-Johnson Syndrome. In clinical studies, the undesirable effects profile was similar in patients treated with rofecoxib for one year or longer. The following serious adverse effects have been reported in association with the use of NSAIDs and cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome, hepatotoxicity includi hepatic failure and jaundice.

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Tablets 12.5 mg and 25 mg: packs of 28 tablets: £21.58. Oral Suspensi 12.5 mg/5 ml and 25 mg/5 ml: bottles of 150 ml: £23.12

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References:

1 Bombardier C, Laine L, Reicin A et al. Comparison of upp gastro-intestinal toxicity of rofecoxib and naproxen in patients w rheumatoid arthritis. *N Engl J Med* 2000;343(21):1520-1528

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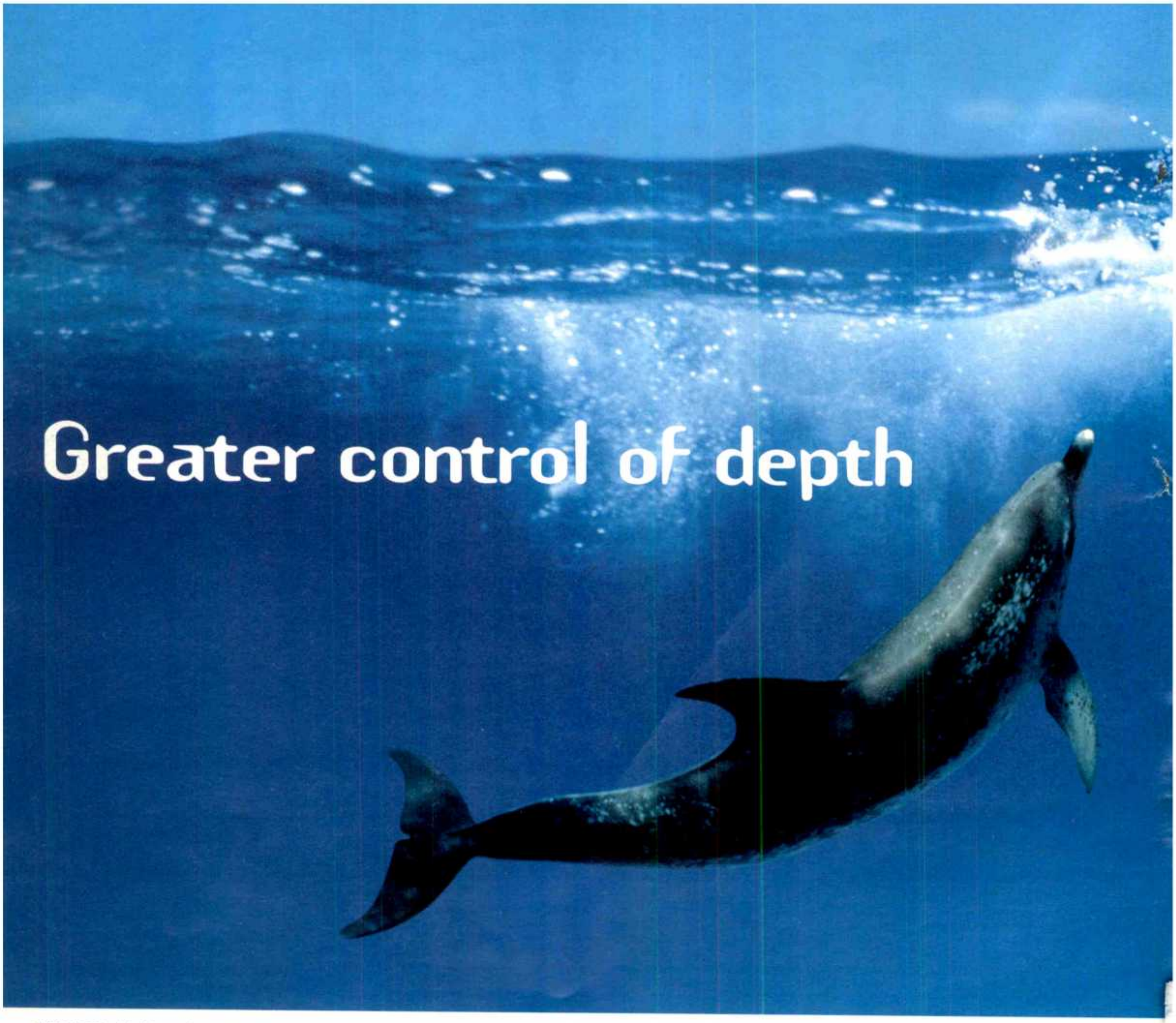
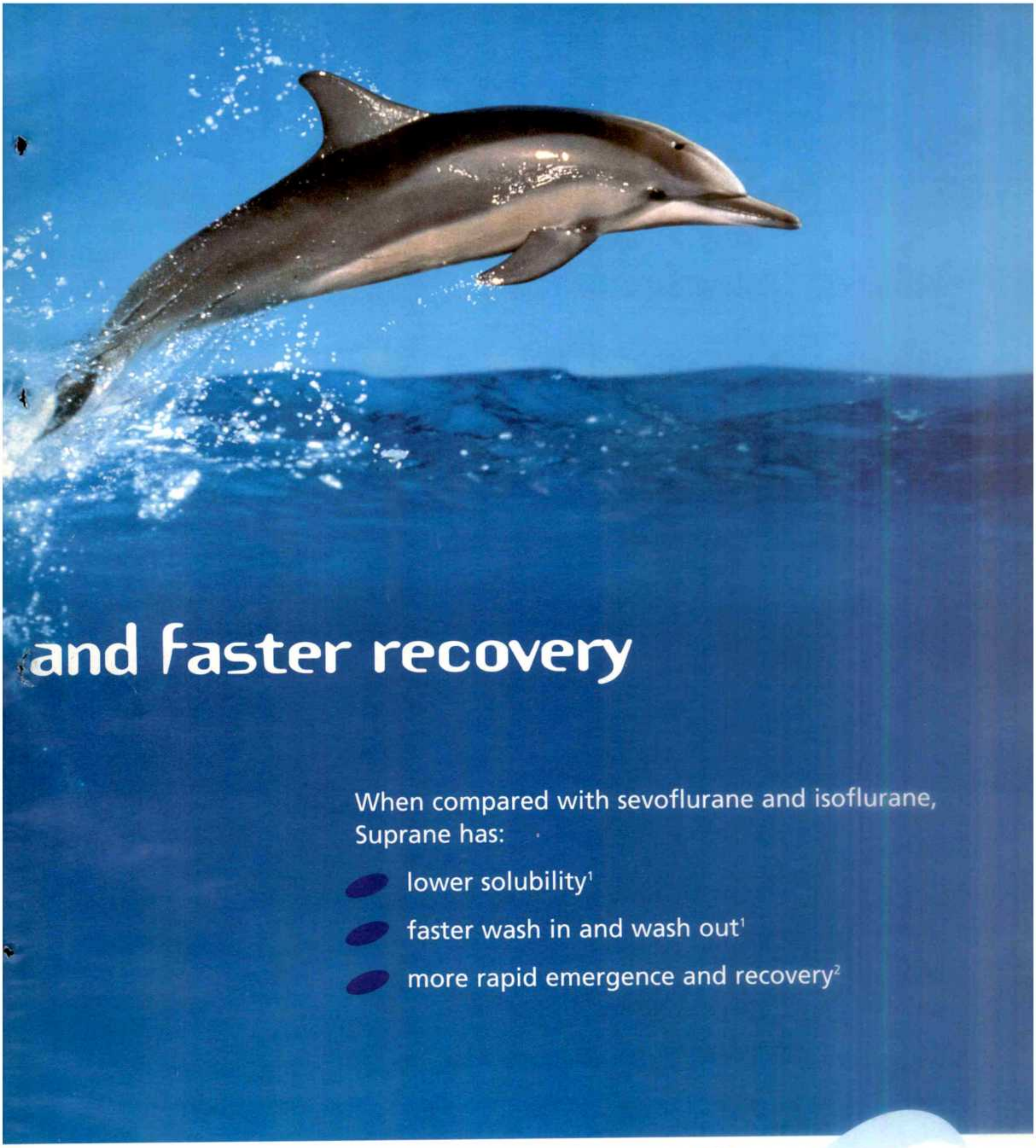


SUPRANE® (desflurane) PRESCRIBING INFORMATION
Presentation: Amber glass bottle containing 240ml desflurane, supplied as pure drug substance. Suprane is a volatile liquid for administration by inhalation. Store in an upright position at room temperature (25°C). **Indication:** Inhalation agent for induction and/or, maintenance of anaesthesia for inpatient and outpatient surgery in adults and maintenance of anaesthesia for inpatient and outpatient paediatric surgery. **Dosage:** Suprane should be administered by trained anaesthetists using a specific vaporiser designed for Suprane. MAC is age-specific and decreases with increasing age. *Induction.* Inspired concentrations of 4-11% of Suprane usually produce surgical anaesthesia in 2-4 minutes. Suprane is not recommended for paediatric induction. *Maintenance.* Surgical anaesthesia may be sustained with 2-6% Suprane when nitrous oxide is used concomitantly. Suprane at 2.5-8.5% may be required when administered using oxygen or oxygen enriched air. Concentrations of up to 18% Suprane have been administered for short periods of time, but if high concentrations are used with nitrous oxide, ensure that the inspired mixture contains a minimum of 25% oxygen. Concentrations of 1-4% in nitrous oxide/oxygen have been used successfully in patients with chronic renal/hepatic impairment. **Contraindications:** Suprane should not be used in patients in whom general anaesthesia is contraindicated, in patients with known hypersensitivity to halogenated agents, or in patients with known or genetic susceptibility to malignant hyperthermia. Suprane should not be used for induction in patients at risk of coronary artery disease or where increases in heart rate or blood pressure are undesirable. **Precautions:** Suprane is not recommended for paediatr induction, or for use in neurosurgical patients. Suprane may increase CSF or intracranial pressure in patients with space occupying lesions. A lower concentration is recommended for hypovolaemic, hypotensive and debilitated patients. Sensitivity hepatitis may be caused in patients previously sensitised b exposure to other halogenated anaesthetics. Suprane has been shown to trigger malignant hyperthermia. To minimise the risk of formation of carbon monoxide in rebreathing circuits, carbon dioxide absorbents should not be allowed to dry out. Suprane is not indicated during pregnancy or breast



When compared with sevoflurane and isoflurane, Suprane has:

- lower solubility[1]
- faster wash in and wash out[1]
- more rapid emergence and recovery[2]

feeding. **Side effects:** Suprane may cause dose-dependent cardio-respiratory depression. Nausea and vomiting have been observed. Hepatitis may occur in patients sensitised by prior exposure to halogenated anaesthetics. In adult induction, cough, breath holding, laryngospasm, apnoea and salivation have been reported. Transient elevations in white blood cell count have been observed. Rare cases of malignant hyperthermia have been reported. No information exists on the effects of Suprane on the ability to drive or operate machinery. An adequate period, at least 24 hours, is needed to ensure full recovery. **Interactions:** Suprane potentiates commonly used muscle relaxants. Lower doses of Suprane are required in those receiving opioids, benzodiazepines, other sedatives, and nitrous oxide. **Overdose:** There is no experience of overdose in humans. Please consult Summary of Product Characteristics for recommendations in the case of overdosing. **Legal category:** POM. **Packs:** Suprane 240ml in amber glass bottles. **Basic NHS price:** £44.41 per bottle. **PL number:** 0116/0327. **PL holder:** Baxter Healthcare Ltd., Caxton Way, Thetford, Norfolk IP24 3SE. **Date of preparation:** December 1999.

® Denotes registered trademark.

References: 1. Eger E I. Anesth. Review. 1993;**20**:87-92. 2. Dupont I et al. Br J Anaesth. 1999;**82**:355-359.

Baxter Healthcare Ltd., Wallingford Road, Compton, Nr. Newbury, Berkshire. RG20 7QW. Tel: 01635 206000

Suprane®
desflurane

Precise control in maintenance anaesthesia

SUP021/UK/0200

EPREX® ABBREVIATED PRESCRIBING INFORMATION

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use; increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM.

Product licence/authorisation holder:
Janssen-Cilag Ltd. Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK.
(PL/0242/0215, 0218, 0221, 0297-9 PA/748/25/1-9)

Date of preparation: February 2000

Further information: Available from:
Janssen-Cilag Ltd. Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK.

APIVERSURGERY01022000

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EPREX® (epoetin alfa) Increases Preoperative Haemoglobin Levels[1,2]

EPREX Maintains Higher Postoperative Haemoglobin Levels[1,2]

Higher Haemoglobin Results In
Reduction in transfusions[1,2]
Improved early postoperative vigour[3]
Earlier participation in rehabilitation[3]

EPREX Is Generally Well Tolerated

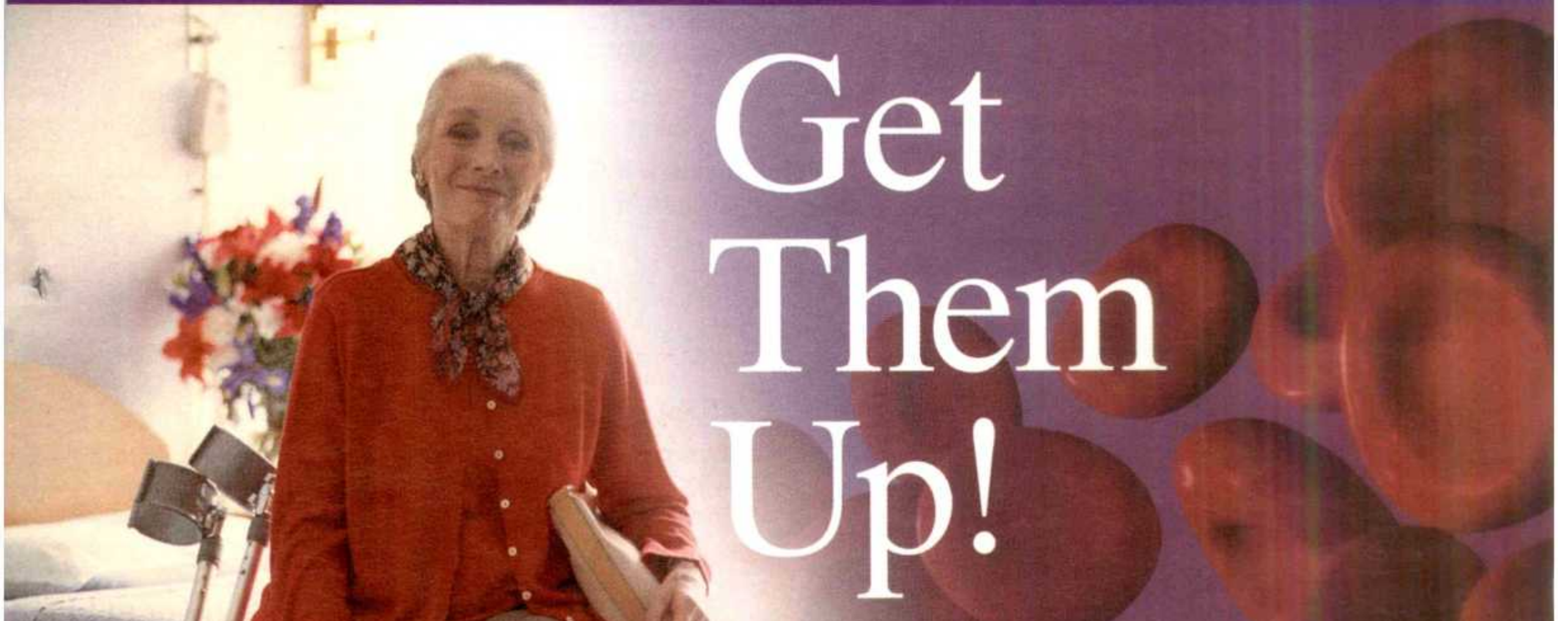
*Haemoglobin levels >10 to ≤13 g/dL.

References:
1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz MC. *Orthopedics.* 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

Please see abbreviated Prescribing Information on adjacent page.

In moderately anaemic patients scheduled for orthopaedic surgery*

HIGHER HAEMOGLOBIN LEVELS MAKE A DIFFERENCE



EPREX®

epoetin alfa

01133

Editorial Notices

STRUCTURED ABSTRACTS

From January 2002, the Summary of all Clinical Investigations, Laboratory Investigations and Short Communications (but not Reviews, Case Reports or Commentaries) published in the *British Journal of Anaesthesia* will be structured under the headings:

Background
Methods
Results
Conclusions

All new manuscripts submitted to the *British Journal of Anaesthesia* from 1 May, 2001 should therefore be presented in this format. If an Editor asks for a revised version of a previously submitted manuscript, please change the Summary in your next draft to the new structured format.

Jennifer M. Hunter
Editor-in-Chief

$500,000 IARS Frontiers in Anesthesia Research Award—Fourth Recipient

The Board of Trustees of the International Anesthesia Research Society (IARS) announced at the 75th Clinical and Scientific Congress the fourth recipient of the $500,000 IARS Frontiers in Anesthesia Research Award. The award was established by the IARS in 1994 'to foster innovation and creativity by an individual scientist in the field of Anesthesiology'. The fourth recipient is:
Mark A. Schumacher, PhD, MD, University of California, San Francisco, California.

Dr Schumacher's research project is titled 'Stretch-Inactivated Channels in Pain Transduction'. Dr Schumacher is an Assistant Professor in the Department of Anesthesia and Perioperative Care at the School of Medicine, University of California, San Francisco.

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Ventilation Through the Ages

ERMEC, Hull Royal Infirmary, Hull, UK, September 10–12, 2001

International ventilation conference covering all aspects of respiratory support from neonates through to adulthood.

To be placed on the list for registration details, please contact: Sue Hubbard, ERMEC, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ, UK. Tel +44 (0)1482 674007; Fax: +44 (0)1482 586587; E-mail: suehermec@hotmail.com

ESRA XX Annual Congress

(European Society of Regional Anaesthesia)
Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Société Française d'Anesthésie et de Réanimation

Annual congresses will take place in Palais des Congrés, Porte Maillot, Paris on the following dates:

September 20–23, 2001
September 26–29, 2002
September 18–21, 2003
September 20–October 3, 2004
September 29–October 2, 2005

For further information, please contact: SFAR, 74, rue Raynouard, F-75016 Paris, France. Tel: +33 1 45 25 82 25; Fax: +33 1 40 50 35 22; E-mail SFAR@invivo.edu

Refresher Course in Anaesthesiology

Durban, South Africa, September 22–23, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

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Second All Africa Anaesthesia Congress in conjunction with the National Congress of the South African Society of Anaesthesiologists

Durban, South Africa, September 23–26, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 2604472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Final FRCA Revision Course

Leicester, UK, October 2–5, 2001

An intensive revision course for the Final FRCA based on small group tutorials and including written and oral examination practice will be held at Leicester Royal Infirmary. Fees: £290 non-residential (including lunch and refreshments); £390 residential (including lunch and refreshments). Course director is Dr Jonathan Thompson. Places are strictly limited. Please telephone Christine Gethins on +44 (0) 116 258 5291 (anae@le.ac.uk) for a booking form.

Dingle 2001—3rd Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 3–7, 2001

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

4th SW Thames Anaesthesia Forum

Da Balaia, The Algarve, Portugal, October 8–11, 2001

The scientific programme will include lectures and discussions on: Acute and Chronic Pain; Paediatric Update; Obstetric Anaesthesia; Neurology and Anaesthesia; ITU and Relevant Medical Topics; Cardiothoracic Anaesthesia; Day Case Surgery; Regional Blocks; New Drugs Update; Training and Education; Information Technology; Free Papers. New! Core Topics for your Personal Portfolio. Guest Speakers, Videos on new Drugs, Equipment and Techniques.

Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: September 1, 2001. Meeting approved for CEPD.

For full information and to secure a place, please visit: www.anaesthesiaupdates.com or contact: Dr J. B. Liban, Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT. Tel: +44 (0) 208725 0018; Fax: +44 (0) 208725 3135; E-mail: liban@mailbox.co.uk

Annual Meeting of the International Society for Anaesthetic Pharmacology (ISAP) (formerly SIVA)

New Orleans, Louisiana, October 12, 2001

For further information contact: International Society for Anaesthetic Pharmacology (ISAP), 2 Summit Park Drive, Suite 140, Cleveland, OH 44131-2553, USA. Tel: +1 216 447 7862; Fax: +1 216 642 1127; E-mail: larshq@iars.org; Web address: www.isaponline.org

The Royal College of Anaesthetists Senior Fellows Club Inaugural Meeting

Royal College of Anaesthetists, Thursday, October 24, 2001 (11.30–14.00)

Speaker: Dr John Nunn 'Climate change and extinction'

This meeting is open to anyone retired from full-time anaesthetic practice who has been associated with the college. The president will give a brief summary of current collegiate activities. Cost £15 to cover buffet lunch and drinks. Places are limited.

Apply to Mrs Mandie Kelly, The Royal College of Anaesthetists, 48/49 Russell Square, London WC1B 4JY, UK.

Tel: +44 (0)20 7813 1900. Fax: +44 (0)20 7813 1876. E-mail: mkelly@rcoa.ac.uk

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

ENT Anaesthesia

London, UK, November 1–2, 2001

A limited number of places are available on a course organized by Dr Ariel Patel and Dr Catrion Ferguson for the Institute of Laryngology and Otology, Royal Free and University College Medical School and Royal National Throat, Nose and Ear Hospital.

For further information, please contact: Joy Gibney or Charmaine Henry, Administration, Institute of Laryngology and Otology, 330–336 Grays Inn Road, London WC1X 8EE, UK. Tel: +44 (0)20 7915 1514/92; Fax: +44 (0)20 7837 9279; E-mail: j.gibney@ucl.ac.uk/c.henry@ucl.ac.uk

5th Annual Conference of the Indian Association of Cardiovascular and Thoracic Anaesthesiologists

Bangalore, India, November 2–4, 2001

It is hoped that there will be a CMF in cardiac anaesthesia on one day preceding the conference, for the benefit of the postgraduate students.

For further information, please contact: Dr Suresh K. Ghaste, Organising Secretary, VIACTA Conference, Professor and Head of Department of Anaesthesiology, Sri Jayadeva Institute of Cardiology, M. H. Complex, Bangalore, S60 002, India. Tel: + 0 6707575 Ex. 138, E-mail: skghaste@yahoo.com

European One Day Course in Spinal Endoscopy

Bradford Royal Infirmary, England, November 9, 2001

This course will be of interest to all those involved with central neural blocks and especially to those involved with the investigation and management of patients with back and radicular pain.

For further information and to secure a place please contact: Dr J. Richardson, MERIT Centre, Bradford Royal Infirmary, Bradford BD9 6RJ, England. Tel: +44 (0) 1274 364271; Fax: +44 (0) 1274 366811

International Scientific Meeting to celebrate the retirement of Professor R. S. Jones OBE, after 40 years in Veterinary Anaesthesia

The Racecourse, Chester, UK, December 6–7, 2001

Theme for the first day: 'Forty Years of Veterinary Anaesthesia'.
Theme for the second day: 'One Vet's Multidisciplinary Contributions'.

For further details please contact: Professor J. M. Hunter. Tel: +44 (0)151 706 4008; Fax: +44 (0)151 706 5884; E-mail: jwa@liv.ac.uk

3rd National Conference Indian Society of Neuroanaesthesiology and Critical Care (ISNACC–2002)

Mumbal, India, January 12–13, 2002

For further details contact: Dr (Mrs) Kanchan S. Jagger, Room No. 423, 4th Floor, Department of Anaesthesia, L.T.M. Medical College Sion, Mumbal: 400022, India. Tel: +91 22 4022976 (O), +91 22 4371811 (R); Fax: +91 22 4076100; E-mail: kanchanjagger@yahoo.co.uk or isnacc2002@sify.com

20th Annual Symposium Clinical Update in Anaesthesiology and Advances in Techniques of Cardiopulmonary Bypass

Paradise Island, Bahamas, January 13–19, 2002

Abstract, Poster and Free Papers Information: (**Deadline – November 1, 2001**) Helen Phillips, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1010, New York, NY 10029-6574, USA. Tel: +1 212 241 7467; Fax: +1 212 426 2009; E-mail: helen.phillips@mssm.edu

13th SW Thames Anaesthesia Update

Belle Plagne, French Alps, January 28–February 1, 2002

The scientific programme will include lectures and discussions on: Acute and Chronic Pain; Paediatric Update; Obstetric Anaesthesia; Neurology and Anaesthesia; ITU and Relevant Medical Topics; Cardiothoracic Anaesthesia; Day Case Surgery; Regional Blocks; New Drugs Update; Training and Education; Information Technology; Free Papers. Case Presentation Competition. Guest Speakers, Workshops, Videos on new Drugs, Equipment and Techniques.

Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: December 10, 2001. Meeting approved for CEPD.

For full information and to secure a place please contact: Dr J. B. Liban, Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT. Tel: +44 (0) 208725 0018; Fax: +44 (0) 208725 3135; E-mail: liban@mailbox. co.uk; Website: www.anaesthesiaupdates.com

International Anaesthesia Research Society Annual Clinical and Scientific Congresses

March 16–20, 2002

IARS 76th Clinical and Scientific Congress, San Diego Marriott Hotel & Marina, San Diego, California, USA.

March 22–26, 2003

IARS 77th Clinical and Scientific Congress, New Orleans Marriott, New Orleans, Louisiana, USA.

March 27–31, 2004

IARS 78th Clinical and Scientific Congress, Tampa Marriott Waterside Hotel, Tampa, Florida, USA.

March 11–15, 2005

IARS 79th Clinical and Scientific Congress, Hilton Hawaiian Village, Honolulu, Hawaii, USA.

Contact information: IARS, 2 Summit Park Drive, Suite 140, Cleveland, OH 44131, USA. Tel: +1 216 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Web: www.iars.org

5th EuroSIVA meeting on Intravenous Anaesthesia

Hotel Le Méridien Nice, 1 Promenade des Anglais, Nice, France, April 5–6, 2002

For further information and registration, please visit the website: www.eurosiva.org or E-mail: registration@eurosiva.org; Fax: +31 71 5248230

Australian and New Zealand College of Anaesthetists Annual Meeting

Brisbane Convention and Exhibition Centre, Brisbane, Australia, May 11–15, 2002

For further information please contact:

ANZCA 2002 Secretariat, PO Box 1280, Milton QLD 4064, Australia.

Tel: +61 (0) 7 3858 5537; Fax: +61 (0) 7 3858 5510; E-mail: anzca2002@im.com.au; Website: www.anzca.edu.au

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Dingle 2002—4th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 2–6, 2002

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

Australian Society of Anaesthetists National Scientific Congress

Adelaide, Australia, October 26–30, 2002

This is the Society's premier scientific conference, held in an interesting part of the world.

For further details, please contact: Festival City Conventions, P.O. Box 949, Kent Town, S.A. 5071, Australia. Tel: +61 (0)8 8363 1307; Fax: +61 (0)8 8363 1604: E-mail: asa2002@fccconventions.com.au

8th International Congress of Cardiothoracic and Vascular Anesthesia
19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:

8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H. Rosenberg, Helsinki University Hospital, Helsinki FIN-00029 HUS, Finland.

E-mail: per.rosenberg@hus.fi
Or: CONGREX/Blue & White Conferences Oy

E-mail: congrex@congrex.fi
Web address: www.congrex.fi

Dingle 2003—5th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 1–5, 2003

For further information contact:

Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

Austrian International Congress 2001 and Rudolf Kucher Forum

Anaesthesia & Intensive Care: The Emerging Discipline
September 12–14, 2001 Vienna, Austria

BJA subscribers will not receive print copies of this Abstract Book, but the abstracts will be available online in September 2001, see http://bja.oupjournals.org. Congress delegates will receive print copies at the meeting. Extra print copies may be ordered for despatch in September 2001 from the Journals Subscriptions Department (Tel. +44 (0)1865 267907, Fax. +44 (0)1865 267485, email: jnls.cust.serv@oup.co.uk), price £24/US$38.

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XEFO® (LORNOXICAM) INJECTION AND TABLETS

Prescribing information (refer to Summary of Product Characteristics before prescribing). **Presentations:** Xefo 8mg Powder for Injection - 10ml vial containing lornoxicam 8.6mg. Xefo Tablets - Film-coated tablets containing lornoxicam 4mg or 8mg. **Uses and Dosage:** Moderate post-operative pain (short-term) - Tablets: 8-16mg daily (maximum single dose 8mg). Injection (iv or im): give in 8mg doses, up to 16mg daily although an additional 8mg dose may be given in first 24 hours. Limit treatment to 2 days. Pain associated with acute lumbo-sciatica - Tablets: 8-16mg daily (maximum single dose 8mg). Injection (iv or im): 8mg twice daily for 1-2 days. Pain and inflammation in osteoarthritis and rheumatoid arthritis. - Tablets: 12mg daily in 2-3 divided doses. Injection and Tablets not indicated for children (<18 years). Injection not indicated for adults aged 65 years or over. **Contra-indications:** Allergy, hypersensitivity, peptic ulceration, severe renal impairment, pregnancy or lactation. **Warnings and precautions:** Mild-moderate renal impairment, liver disease, coagulation disorders, hypertension or obesity, long term treatment (>3 months), elderly patients. Monitor renal function in patients undergoing major surgery, with stressed renal function, cardiac failure, on diuretics or taking concomitant treatment suspected of causing renal damage. **Undesirable effects:** Frequency 1-10%. Tablets: Abdominal pain, diarrhoea, dizziness, dyspepsia, headache, nausea and vomiting. Injection: Abdominal pain, dizziness, fatigue, headache, injection site reactions, nausea, somnolence. See SPCs for details of adverse reactions occurring with frequency of less than 1%. **Legal categories, marketing authorisation numbers, package quantities and prices:** Xefo 8mg Powder for Injection: POM. PL 18467/0008. 1 vial - £2.25. Xefo 8mg Tablets: POM. PL 18467/0007. 30 tablets - £8.85. Xefo 4mg Tablets: POM. PL 18467/0006. 30 tablets - £8.85. **Marketing authorisation holder:** CeNeS Limited, Compass House, Vision Park, Chivers Way, Histon, Cambridge CB4 9ZR. Date of preparation: July 2001. **References:** 1. Norholt SE, *et al. Pain* 1996; **67**: 335-343. 2. Ilias W, Jansen M. *Br J Clin Pract* 1996; **50** (4): 197-202. 3. Rosenow DE, van Krieken F, Stolke D, Kursten FW. *Clin Drug Invest* 1996; **11** (1): 11-19. 4. Kidd B, Frenzel W. *J Rheum* 1996; **23** (9): 1605-1611. 5. Comprehensive evaluation of safety data in patients treated with lornoxicam. Data on file 1995. Eagle image © Dorling Kindersley.

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Abbreviated version of the International summary of product characteristics Therapeutic indications*: Esmeron is indicated as an adjunct to general anesthesia to facilitate tracheal intubation during routine and rapid sequence induction, and to provide skeletal muscle relaxation during surgery. Esmeron is also indicated as an adjunct in the intensive care unit (ICU) to facilitate tracheal intubation and mechanical ventilation. **Contra-indications** Former anaphylactic reactions to rocuronium or to the bromide ion. **Special warnings and special precautions for use** Since Esmeron causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this drug until adequate spontaneous respiration is restored. As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique. Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Esmeron, have been reported. These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume that they may occur and take the necessary precautions. Dose levels greater than 0.9 mg rocuronium bromide per kg body weight may increase the heart rate; this effect could counteract the bradycardia produced by other anesthetic agents or by vagal stimulation. In general, following long term use of muscle relaxants in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of muscle relaxants. In addition, patients should receive adequate analgesia and sedation. Furthermore, muscle relaxants should be titrated to effect in the individual patients by or under supervision of experienced clinicians who are familiar with their actions and with appropriate neuromuscular monitoring techniques. Because Esmeron is always used with other agents and because the occurrence of malignant hyperthermia during anesthesia is possible, even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anesthesia. In animal studies, Esmeron was shown not to be a triggering factor for malignant hyperthermia. **The following conditions may influence the pharmacokinetics and/or pharmacodynamics of Esmeron:** *Hepatic and/or biliary tract disease and renal failure.* Because rocuronium is excreted in urine (up to approximately 30% within 12-24 hours) and it is expected that it is also partly excreted in bile, Esmeron should be used with caution in patients with clinically significant hepatic and/or biliary diseases and/or renal failure. In these patient groups prolongation of action has been observed with doses of 0.6 mg rocuronium bromide per kg body weight. *Prolonged circulation time.* Conditions associated with prolonged circulation time such as cardiovascular disease, old age and edematous state resulting in an increased volume of distribution, may contribute to a slower onset of action. *Neuromuscular disease.* Like other neuromuscular blocking agents, Esmeron should be used with extreme caution in patients with a neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or with the myasthenic (Eaton-Lambert) syndrome, small doses of Esmeron may have profound effects and Esmeron should be titrated to the response. *Hypothermia.* In surgery under hypothermic conditions, the neuromuscular blocking effect of Esmeron is increased and the duration prolonged. *Obesity.* Like other neuromuscular blocking agents, Esmeron may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients, when the administered doses are calculated on actual body weight. *Burns.* Patients with burns are known to develop resistance to non-depolarizing neuromuscular blocking agents. It is recommended that the dose is titrated to response. **Conditions which may increase the effects of Esmeron** Hypokalemia (e.g. after severe vomiting, diarrhea and diuretic therapy), hypermagnesemia, hypocalcemia (after massive transfusions), hypoproteinemia, dehydration, acidosis, hypercapnia, cachexia. Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible. Therapeutic indications may vary from country to country. *For full prescribing information see your local package insert. December 1999

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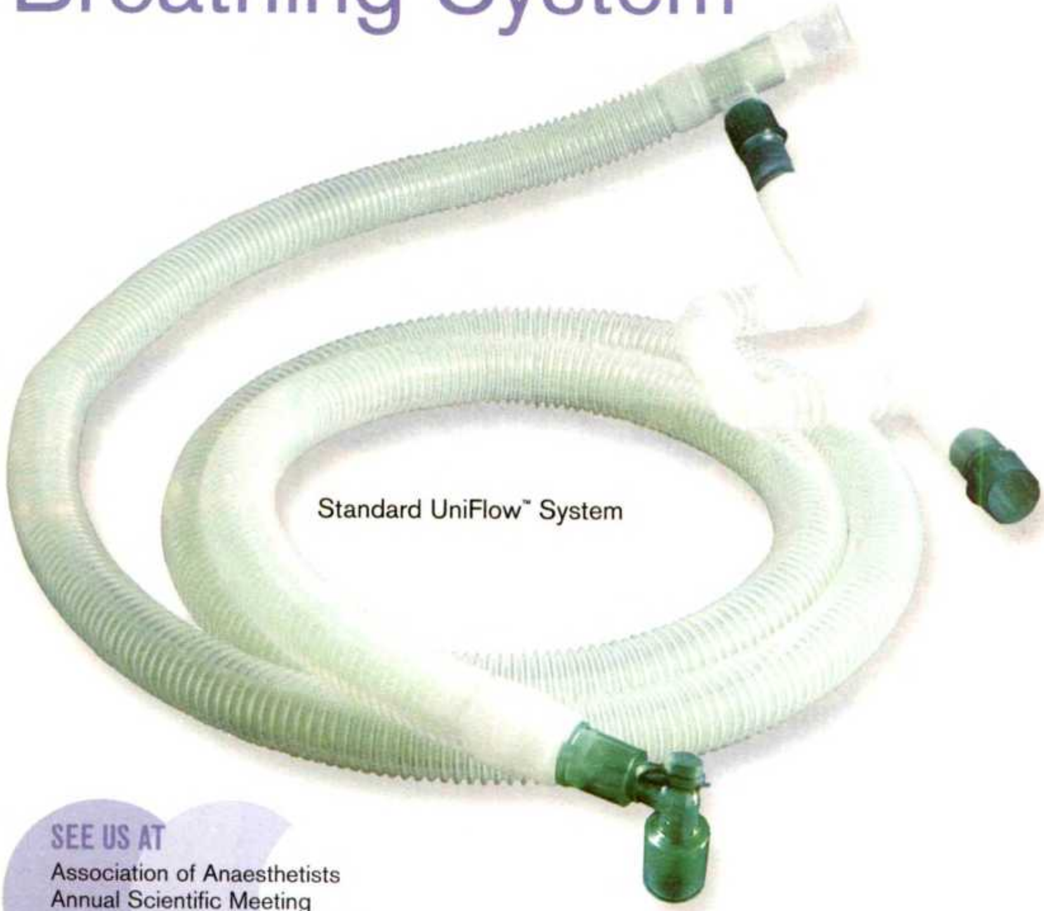

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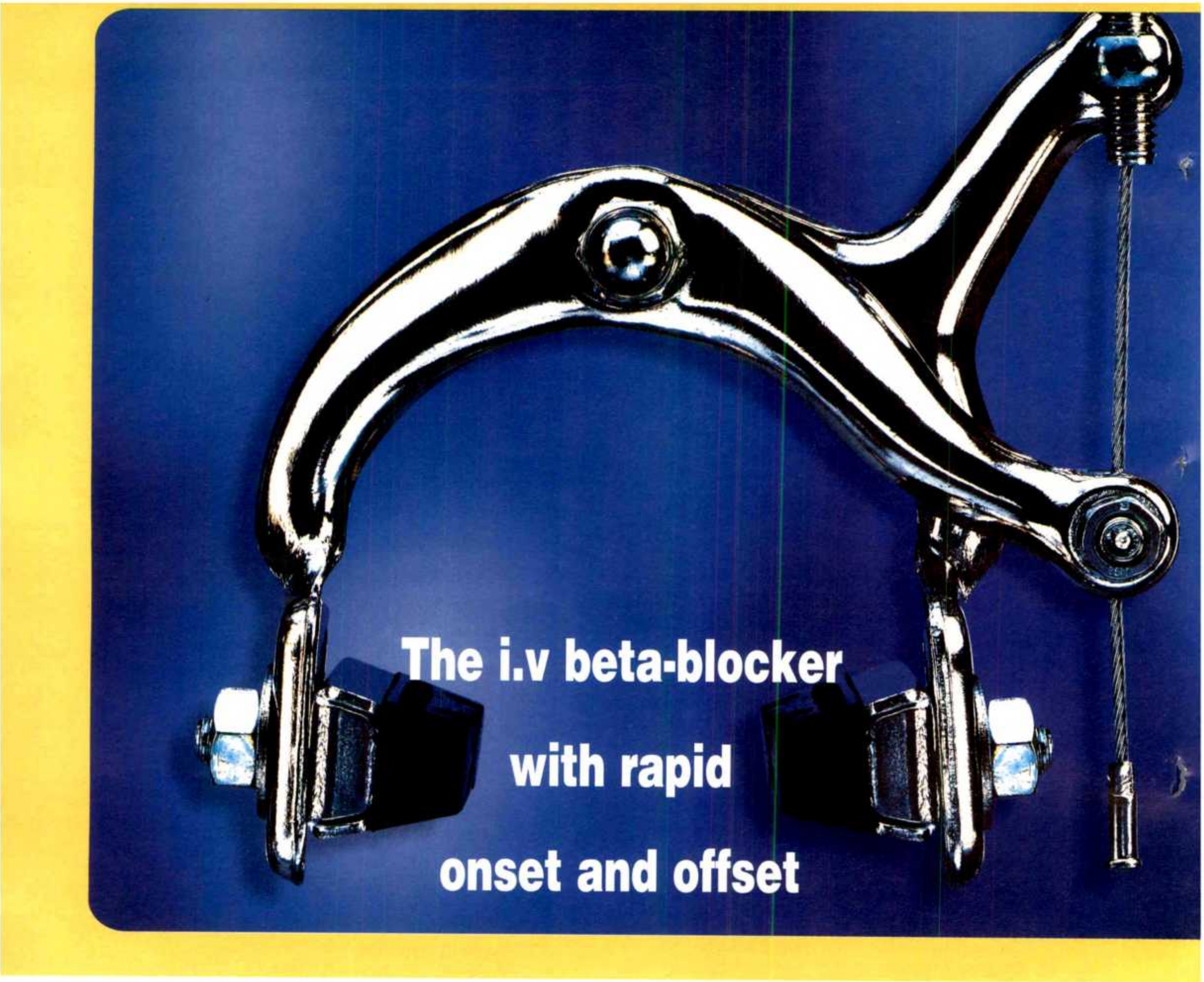

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BRITISH JOURNAL OF ANAESTHESIA

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Editorial I

Evidence based practice in intensive care—light on the horizon?

The practice of intensive care medicine, although now on a much firmer footing, is nevertheless an emerging speciality. Foundations were laid in the 1950s, and although other countries were ahead, this at present multidisciplinary practice has only recently gained speciality recognition within the UK from the Specialist Training Authority (STA). It would have been expected that such a new speciality would have been entirely governed along the modern evidence based practice system. This, however, is not the case. It is perhaps the perception from those not working in intensive care that those practitioners who do are reluctant to be guided along evidence based medicine practice and critical care medicine is consequently lagging behind other areas of medical practice.

A recent Editorial in this journal on parenteral and immunonutrition[1] along with the subsequent letters of rebuttal and a reply from the original authors,[2] illustrates the concerns well. The conclusion is that 'many intensivists have a voracious appetite for novel unproven therapies'. To an extent this perception is correct. However, at last, things are about to change.

Undertaking research in critically ill patients is notoriously difficult and, therefore, much of the original and groundbreaking work in the speciality has involved animal models. These have been useful to an extent but as much of the practice of intensive care involves multiple disease processes, animal models cannot precisely mimic the human situation. Mice are not men. Nowhere is this more apparent than in the area of sepsis, which is still a major contributor to mortality on the intensive care unit. Another difficulty, which has perhaps delayed the accumulation of evidence on which to base our practice, is the lack of a single disease entity to study. For example, cardiology is often cited as a good example of a speciality that practices evidence based medicine. However, many of the trials in this area concentrate on very specific conditions and most are funded by the pharmaceutical companies who look to the large potential market to support the costs of the research. The average intensive care unit has a wide range of conditions and patients with varying underlying abnormalities of baseline physiological reserve. It is, therefore, unlikely that a single intervention will influence the outcome of such a diverse population.

Further support for the suggestion that intensive care practitioners are reluctant to wholeheartedly embrace evidence based practice is the widespread hue and cry that has ensued as a result of the recent papers addressing the use of albumin[3] and pulmonary artery catheters.[4] These papers are the results of meta-analyses of a large collection of small studies of varying quality. Although there has been much criticism of both papers, the use of albumin has declined appreciably and more workers are questioning the routine use of pulmonary artery catheters. So perhaps intensivists are willing to alter practice—but not to admit to it.

Of more significance, however, is the very recent appearance of five separate studies all of which will have an impact on intensive care practice. All five reports are the result of large, well-conducted randomized studies involving intensive care patients and all have shown a significant reduction in mortality. Although much of this work is currently only available in abstract format and so has not been through the peer review process, all will result in changes of practice. Perhaps at last there is a light on the horizon for evidence based practice in intensive care.

Mechanical ventilation

The traditional approach to mechanical ventilation has been to use tidal volumes considerably in excess of normal—usually around 10–15 ml kg^{-1}. This has been necessary to correct hypoxia and hypercarbia and prevent atelectasis. However, there has been increasing evidence of the damaging effects of such ventilation patterns from a variety of animal studies. Large tidal volumes in animals are associated with disruption of pulmonary capillary endothelium and alveolar epithelium,[5] lung inflammation, and the systemic release of inflammatory mediators.[6] This latter effect may then result in injury to other organs.[7] Uncontrolled studies in patients with acute lung injury have suggested that the use of lower tidal volumes may be associated with a better outcome. Four small, randomized trials showed conflicting results—there was, therefore, a state of equipoise and clearly a need for a large, well-conducted, randomized trial. Such a trial was designed and conducted and was stopped after an interim analysis because of overwhelming benefit.[8] In this study, 861 patients were

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randomized to either a ventilatory strategy aimed at preventing lung damage or to ventilation at traditional higher tidal volumes. The mortality rate was 39.8% in the traditional ventilation group and 31.0% in the lung protection group (*P*=0.007). The lung protection ventilator strategy used was: a tidal volume of 6 ml kg^{-1} of predicted body weight, reduced by 1 ml kg^{-1} if necessary to maintain plateau pressure <30 cm H_2O; ventilator rate set to 6–35 min^{-1} to achieve a pH goal of 7.3–7.45; and PEEP varied according to inspired oxygen tension using a standard table. This ventilator strategy will now become the gold standard against which all others will be compared and should form the basis for good practice.

Steroids in sepsis

A previous study of high dose steroids concluded that steroids had no place in the management of patients with sepsis as outcome was significantly worse.[9] However, there have been recent reports of the value of lower dose steroids to correct refractory hypotension.[10] There is now a preliminary report of the value of low dose steroids in patients with sepsis, which is the result of a large, randomized controlled trial conducted in France.[11] In this study, 299 patients in septic shock were studied and 229 were found not to respond to a short Synacthen test. Patients were randomized to receive either steroid treatment with hydrocortisone 50 mg intravenously 6 hourly and fludrocortisone 50 mg once per day orally or placebo, for 7 days. There was a 30% decrease in the risk of death following the use of steroids in these patients, with most of this effect being a result of improvements in the non-responder group. Clearly this is an early report of an interesting study, which could well change the standard management of septic shock.

Anti-TNF in sepsis

A monoclonal antibody to tumour necrosis factor-α (TNF-α), one of the early mediators in sepsis, was evaluated a few years ago in three large multinational studies.[12–14] Although initially very promising in animal studies and the early studies in humans, results from three large, randomized studies of the same monoclonal antibody which enrolled a total of 3537 patients with severe sepsis failed to show any statistically significant benefit. Animal models have now allowed us to appreciate the multitude of regulatory processes that interact during sepsis, and also the redundancy involved in this regulation. A lack of appreciation of these facts has probably resulted in the failure of many new treatments in the septic patient. It is, therefore, interesting that an early report of a new study has shown a significant, although small, benefit of a new anti-TNF-α molecule.[15] A total of 2634 patients with sepsis were enrolled into a placebo controlled randomized trial which showed a decrease in mortality from 35.9 to 32.3% (*P*=0.049). The mortality difference is small but the study does at least demonstrate that it is possible to conduct well-designed trials in such a heterogeneous population of patients and demonstrate a statistically significant difference in outcome.

Activated protein C

A number of small studies and case reports have suggested a possible beneficial effect of protein C in patients with severe sepsis. The rationale for using protein C originated because of the coagulopathy often seen in sepsis and the quite significant risk of tissue loss associated with intravascular thrombosis particularly in meningococcal sepsis. Activated protein C has both anti-thrombotic and pro-fibrinolytic activity. Phase II studies confirmed the efficacy of protein C in sepsis with regard to the coagulopathy but were not powered to demonstrate a conclusive mortality benefit. A phase III study of recombinant human activated protein C was halted at an interim analysis and the initial results are currently published only in abstract form.[16] A total of 1690 patients with severe sepsis was enrolled into the study before it was halted and mortality was decreased from 30.83 to 24.72% in the treatment group (*P*=0.0054). The mortality rate in the placebo group of patients is low but not that different to that found in the anti-TNF study. Hopefully, further data analysis of these results will provide more useful information. It is also possible that activated protein C had this beneficial effect via an anti-inflammatory action rather than any effect on the clotting system. It is again clear that a well-conducted trial is possible in the intensive care population. It is possible that this is another approach to the management of patients with sepsis that will change the practice of those working on intensive care.

Renal dose dopamine

Low dose dopamine is commonly used to increase renal blood flow, induce natriuresis and diuresis, and also theoretically to prevent patients developing renal failure by offering renal protection. Although there have been many small trials demonstrating a lack of renal protection, practitioners have continued to use the drug for this purpose and there were emerging worries about the harmful effect of dopamine on pituitary function. A randomized study which enrolled 328 patients has recently been published which should hopefully change current practice.[17] In this study, peak creatinine concentrations and the requirement for renal replacement therapy were identical in those receiving dopamine 2 μg kg^{-1} min^{-1} to those receiving placebo. The accompanying editorial asked us to 'stop hedging and accept that there is no justification for using renal dose dopamine for renal protection'.[18]

Evidence based medicine should be considered more a way of life than simply a way of dictating how patients and clinical problems are managed. It is a process of self-directed learning that should continue throughout our working practice. There are five components to evidence based medicine:

1. identify relevant questions;
2. track down the best evidence to answer these questions;
3. critically appraise the evidence;
4. apply the results of the appraisal to clinical practice; and
5. evaluate performance following the change in practice.

There are many relevant questions that surround the practice of intensive care medicine. However, the best evidence with which to answer these questions has often been missing. Well designed and carefully conducted controlled, randomized and double blind studies, which are adequately powered, are fundamental to the practice of evidence based medicine and it is these which have been lacking.

All five examples demonstrate that it is possible to conduct conclusive studies in the critically ill, despite the wide mix of underlying pathology and baseline physiological reserve. Intensivists are capable of asking the right questions and undertaking the research to a strictly agreed protocol—both essential parts of evidence based practice. The next step is how to introduce the change in practice on the basis of the studies undertaken. It is this last crucial step that is the hardest. Moreover, how best to implement change, has received little attention in the past. This is the issue for the next few years.

Although we all know that renal dose dopamine does not protect the kidney it is nice to see the urine flowing. But we have to believe what we read following a critical appraisal rather than seeing with our own eyes the volume of liquid in the urine bag. However, we are not alone—some of our surgical colleagues still ask 'have you started the dopamine?'

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Note added in proof

The study by Bernard and colleagues (reference 16) has now been published in full Bernard GR, Vincent JL, Laterre PF, *et al* Efficacy and safety of recombinant activated protein C for severe sepsis *N Engl J Med* 2001, 344· 699–709

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†Conflict of interest: Professor N. R. Webster is a member of the Zovant® Advisory Board of Eli Lilly UK

Editorial II

Fatty acid amides are putative endogenous ligands for anaesthetic recognition sites in mammalian CNS

'To sleep, perchance to dream' W. *Shakespeare*

The pioneering work of Meyer and, concurrently but independently, Overton over a century ago, demonstrated that the potency of anaesthetics within a homologous series correlated with their ability to partition out of aqueous solvents into lipids such as octanol. This suggested to several generations of researchers pursuing mechanisms of action, that the molecules were exerting a non-selective physical perturbation of a lipid site in membranes or possibly perturbing the volume or fluidity of the plasma membrane itself.[1] Lipid theories of anaesthetic action have been increasingly marginalized by researchers uncovering substantive evidence that proteins (first the globular luciferases, then, increasingly, native or recombinant ion channels) can bear saturable stereoselective sites for modulation by 'clinical concentrations' of a broad spectrum of anaesthetic drugs.[2] Furthermore, these drugs exhibit the same structure–activity profiles *in vitro* at the channel targets as they do in patients.[3] Perhaps the most attractive model targets for anaesthetic action are the ligand-gated ion channels (LGIC), particularly the nicotinic receptor superfamily.[2] All the members of this family (nicotinic, $5HT_3$, glycine, and $GABA_A$ receptors) are thought to form fast ion channels by aggregating five subunits around a central hydrophilic pore. This pentameric structure has been confirmed by electron microscopy which suggests that the channels gate (i.e. open when neurotransmitter is bound) via a relatively localized conformational change confined to the core of the protein.[4] Importantly for lipid soluble anaesthetics, during these gating transitions macromolecular subunits themselves do not twist or distort their outer structure at the interface with the membrane bilayer. A plethora of influential papers have recently highlighted the fact that inhibitory ionotropic receptors activated by GABA/glycine have crucial roles in regulating arousal.[5 6] GABA is used as a transmitter at up to one-third of all CNS synapses. The $GABA_A$ receptor probably represents the closest molecular species to a unifying target for general anaesthetics in the brain.[7] With the cloning of the receptor subunits throughout the 1980s and 1990s we now know that their are many 'isoforms' of the $GABA_A$ receptor expressed in the CNS (e.g. see Mckernan and Whiting[8]). Eight GABA subunit classes have been cloned to date, with up to six homologues in each. In the late 1990s it was disclosed that single amino acids (at two discrete intramembranous sites) in ion channel subunits comprising 450 residues conferred sensitivity to volatile anaesthetics, etomidate and ethanol.[5 6] Importantly, these residues were in transmembrane segments of the pentameric channel complex at sites adjacent to or actually lining the ion channel lumen. The above might be interpreted by some as the definitive unifying solution to the question of cellular actions of anaesthesia but it remains to be seen whether the removal of these sites *in vivo* will significantly alter the response of whole animals to such depressant drugs. Confirmation that the 'anaesthetic-sensitive' β2 subunit has been successfully knocked out in non-lethal mutant mice came in a flurry of abstracts at the European Neuroscience meeting (the largest ever held in the UK) in 2000 in Brighton, England. However, no evidence for or against the relevance of these subunits for anaesthetic action *in vivo* has been published to date.

In a wider context, anaesthetics are notoriously low-affinity and non-selective drugs that may underpin the agent-dependent spectrum of pharmacological and toxicological effects seen *in vivo*. Voltage-gated channels and pre-synaptic processes were historically portrayed as relatively insensitive (being blocked only by 'heroic' MAC-multiples).[9] Many of these data were obtained in model (experimentally accessible) preparations such as the squid axon. Thanks to such invertebrate models we know that all voltage-gated pores exist in conformationally distinct modes which underpin action potential shape, unidirectionality and refractoriness: increasingly, it is apparent that the actions/potency of anaesthetics at these pre-synaptic targets are demonstrably state-dependent.

Now it is possible to study cloned voltage-gated Na^+ channels from a variety of species, including humans, under different conditions of neural discharge or in distinctive ionic environments.[10] Mammalian Na^+ channels can be significantly depressed by MAC-equivalent general anaesthetic concentrations if the cells are tonically depolarized or induced to fire rapidly.[11] A variety of voltage-gated calcium channels (VGCCs) are also demonstrably sensitive to block by 1–4 MAC isoflurane.[12] Much of the argument in favour of LGICs as *relevant model* anaesthetic targets hinges on their relatively high-affinity for anaesthetics (EC_{50s} or IC_{50s} are higher for VGCCs).[2 13] This correlates better with MAC-equivalent concentrations of anaesthetics in patients at equilibrium. The VGCC experimenters, or independent reviewers, argue that their data are physiologically relevant based on the very steep Ca^{2+} dependence of transmitter-release. The patch clamp technique devised in the early 1980s is applicable even to the smallest mammalian nerve cell. The pioneering work of Forsythe laid the foundations for impaling both pre-synaptic and post-synaptic cells in the same mammalian CNS synapse. Based on his experiments with metabotropic glutamate receptors, only a tiny proportion of the pre-synaptic Ca^{2+} current needs to be inhibited to impair profoundly the transynaptic signal.[14] This reinforces the potential importance of pre-synaptic Ca^{2+}-entry for clinical anaesthetic effect. To summarize, LGICs are only one of a series of anaesthetic-sensitive signalling proteins in the brain. Voltage-gated K^+ channels, particularly those with 'twin-pore' structures[15] are demonstrably sensitive too. Indeed, elegant mutagenesis experiments have again highlighted important domains for anaesthetic/alcohol recognition on the voltage-gated K^+ channels.[16] The NMDA glutamate receptor has long been acknowledged as a high-affinity and stereoselective target for ketamine[2] and may also be an important target for nitrous oxide[17] and the experimental anaesthetic, xenon.[18] What evidence exists for endogenous modulators of arousal which exert their hormonal actions at these anaesthetic drug recognition sites?

For certain structural classes of anaesthetic there is strong, and in some cases, irrefutable evidence for endogenous ligands. A variety of physiological neurosteroids (e.g. see Belelli and colleagues[19]) have been shown to modulate sites on $GABA_A$ receptors and these may well influence mood and behaviour as their titres change in menstruation and sexual development. When a veterinary surgeon administers alphaxalone to his moribund charges, is he simply administering a lipid soluble membrane perturbing agent or saturating neural receptors geared to sensing the actions of much lower levels of circulating hormones? Pharmaceutical companies and biophysicists have attempted to restore polar alphaxalone derivatives (with no need for toxic excipients) to medical practice in recent years.[20] Thanks to the pioneering work of Hughes, Kosterlitz and coworkers, endorphins and enkephalins are now established as endogenous ligands for clinically useful opiate anaesthetics.[21] Cholesterol has long been known as a depressant, even anaesthetic, molecule in laboratory animals.[22] Interestingly, much play has been made on the stereoselective actions of anaesthetics at the LGIC targets.[2] This stereoselectivity for molecules such as isoflurane (<2-fold shift in potency between diastereoisomers) or even barbiturates (circa 10-fold shift in EC_{50}) is not all or none. Nevertheless, it is almost invariably interpreted as evidence for a selective interaction of the drug with the target protein rather than a non-selective hydrophobic interaction with bulk membrane or interfacial lipids. Cholesterol itself is highly chiral and is well known to be concentrated at the interface between subunit protein and bulk membrane at nicotinic receptors.[23] For recombinant channels in artificial bilayers the presence and concentration of cholesterol is crucial for the functional operation of the ion channel complex.[24]

Another membrane lipid component has attracted considerable recent attention as an endogenous depressant. *cis*-9,10-Octadecenoamide (cOA or 'oleamide') was originally isolated from sleep-deprived cats and an enzyme specific for its hydrolysis is present in rat brain.[25] Synthetic oleamide induced physiological sleep when injected into rats but little is known about its cellular mode of action. High-affinity interactions with recombinant G-protein-linked receptors such as $5HT_2$ or $5HT_7$ have been reported.[26] Conflicting evidence suggests that the hypnogenic effects are probably not secondary to activation of G-proteins.[27] More recent studies demonstrate that oleamide may bind to cannabinoid sites (IC_{50} of 10 μM) in rodent CNS, that it induces hypolocomotion *in vivo* which is sensitive to the CB1 antagonist SR141716A, but that the brain lipid cannot elicit the same second messenger responses as acknowledged CB1 cannabinoid agonists.[28] The low-affinity binding and lack of coupling to cAMP both cast doubt on the relevance of a direct interaction with CB1 receptors. To date, none of these putative receptor interactions have been shown to contribute to a net depressant effect for oleamide at a systems level. Experiments in laboratory animals confirm that oleamide induces sleep and biologically active concentrations of oleamide in CSF have been determined.[29] CB1 antagonists block the oleamide effects on sleep latency in laboratory animals.[30] The endogenous CB1 ligand anandamide and oleamide are both hydrolysed by the same fatty-acid amidohydrolase enzyme. It has been suggested that the hypnogenic effects of oleamide are not receptor mediated but rather they reflect quenching of this enzyme to increase the titre of anandamide or other endocannabinoids. At the cellular level, oleamide has several interesting parallels with general anaesthetics. Recently, we demonstrated that rat $GABA_A$ receptors and inhibitory synaptic currents are sensitive to modulation by oleamide (but not equally hydrophobic congeners such as oleic acid or the non-hypnogenic *trans* isomer). Recombinant human $GABA_A$ receptor isoforms expressed in oocytes were modulated by oleamide and diazepam only if a γ subunit was co-expressed with $\alpha\beta$ (but the fatty acid amide response was insensitive to high concentrations of flumazenil, indicating an independent site of action),[31] see also Yost.[32] The fact that oleamide and anaesthetics differentially modulate ion channel isoforms in an invariant oocyte membrane strongly suggests that they exert their effects on sterically well-defined sites on the protein, rather than the lipid environment of the cell surface. Oleamide enhances currents through all $GABA_A$ and glycine subunit isoforms that we have examined to date (with the exception of $\alpha\beta$ alone which is not thought to be widely expressed in the brain) but it does not modulate currents through the Rho subunit.[33] This subunit was originally cloned from retinal tissue but has since been detected at discrete sites in CNS and is not positively modulated (some labs report antagonism) by inhalation anaesthetics.

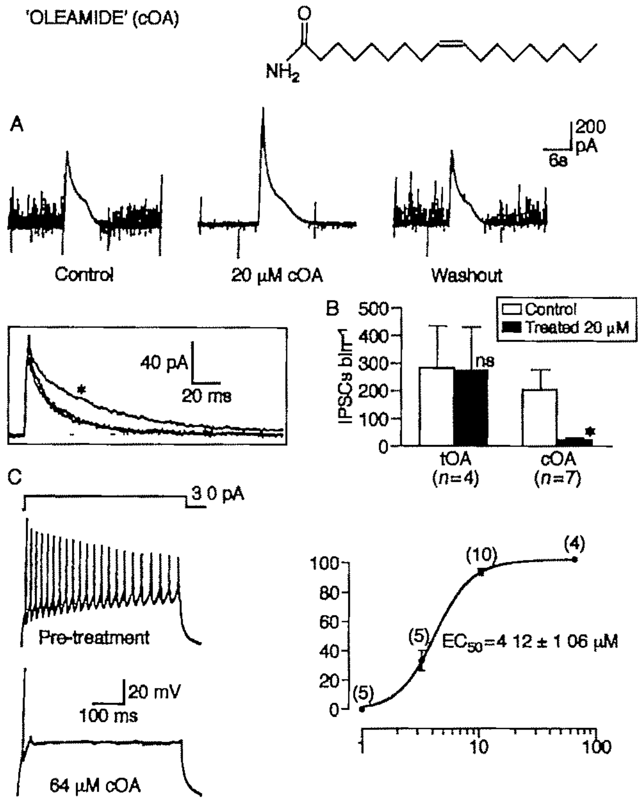

Fig 1 Oleamide is a simple unsaturated fatty acid (C18) amide: the *cis* form of the molecule (shown above) is an active sleep inducer (cOA) but *trans* oleamide (tOA) was not hypnogenic *in vivo*. In common with steroid, barbiturate and volatile anaesthetics, in analogous experiments in our laboratory, the sleep hormone depresses spontaneous activity in cultured neurones and modulates GABA activated chloride currents or prolongs inhibitory synaptic currents. (A) Reversible effects of cOA on responses to 4 s pulses of GABA Note the large increase in evoked currents is co-incident with a drastic reduction in the incidence of synaptic currents (baseline noise). (B) The effects of oleamide such as those of anaesthetics reflect steric conformation: only the *cis* geometric isomer significantly modulates GABA$_A$ currents (not shown) or the incidence of synaptic currents in culture as shown in the bar chart (quantified here for inhibitory synaptic currents or IPSCs but excitatory events, EPSCs, were also affected in this way). The inset depicts the effects of 20 µM cOA (*) on averaged synaptic currents compared with pre-treatment and post-washout IPSC profiles. Modified from references.[31 34] Like anaesthetics, oleamide concurrently targets electrogenesis (pre-synaptic conduction) and depresses transmitter-release from nerve terminals.[34] (C) Bursts of tetrodotoxin-sensitive action potentials are blocked by cOA but not tOA (not shown). The primary spike is not impaired even at high doses. The suppression of these sodium spikes is exerted in the low micromolar range (right) Voltage-clamp experiments confirm that, like a variety of anaesthetics, cOA promotes channel inactivation and retards recovery from the inactivated state. These voltage-clamp data (not shown here) have been published in *Anesthesiology*.[35]

We have since shown that oleamide concurrently, and with slightly higher affinity, can depress pre-synaptic function, transmitter-release and neuronal burst firing by a state-dependent interaction with the voltage-gated Na$^+$-channel (Fig. 1).[34] In voltage-clamped mouse channels, the brain lipid exerts a spectrum of effects closely akin to those exerted by a variety of anaesthetics at clinical concentrations.[35] The depressant molecules exert some degree of tonic block (more pronounced at depolarized holding potentials), shift inactivation curves strongly in the hyperpolarizing direction and retard recovery from the inactivated channel state. Oleamide, possibly because of its extreme hydrophobicity, does not exhibit frequency-dependent facilitation of block unlike general/local anaesthetics and anticonvulsant drugs.[36] At both the GABA$_A$ receptor and the Na$^+$ channel oleamide is highly stereoselective in its actions.[34] Only the hypnogenic *cis* form of the molecule exerts a modulatory response (the *trans* form of the molecule was not effective as a sleep inducer[25] and cannot suppress spontaneous activity in our model cultured neurones). However, the actions of *cis* oleamide are selective amongst ion channels as it does not block glutamate currents even at high doses and it modulates K$^+$ channels only at high concentrations (some were weakly antagonized, other unidentified currents enhanced: to our knowledge, twin-pore channels have yet to be examined but oleamide does not directly alter neuronal or synaptosoneurosomal resting potential). To summarize the above profile, oleamide exerts stereoselective interactions with target ion channels, which are broadly consistent with its depressant actions and with those of structurally divergent anaesthetics. Like most anaesthetics, it can disrupt post-synaptic function at inhibitory ion channels (but not excitatory channels): pre-synaptic transmitter-release and conduction are reduced by depressing currents through voltage-gated pores. At high concentrations (>20 µM) other groups report that oleamide can deconvolute gap junctions in glia.[37] Gap junctions underpin direct electrical coupling in glial syncitia but are probably more familiar to physiologists or anaesthetists as key components in conducting pathways in the myocardium. Supra-clinical concentrations of anaesthetics can also block gap junctions, for example in fast neural relays underpinning high frequency oscillations in the EEG.[38] If anaesthetics do target similar sites, both the voltage-gated channels and the gap junctions in cardiac tissue could underpin some of the cardiodepressant and arrhythmogenic side-effects seen in patients.

It is already apparent that oleamide itself is not a potent anaesthetic, nor does it strongly synergize anaesthetic drugs in laboratory animals.[32] We know that there is a significant pharmacokinetic and distribution problem when exogenous oleamide is administered to animals. A variety of centres found it difficult to reproduce the original Scripps data on sleep by intraperitoneal administration[39] but recent studies confirm the acute psychomotor depression and hypnogenic effects (e.g. see Cheer and colleagues[40]). An important determinant of activity is the inclusion of carrier lipid in the formulation administered suggesting this may quench degradation of the drug.[41] Under these conditions oleamide can synergize benzodiazepines and barbiturates.[30] Like other amides exposed to serum or CSF amidohydrolases (e.g. local anaesthetics) the molecule will be cleaved readily. Even by direct injection into the ventricular system of the brain, the molecule will not distribute widely or evenly because of its extremely hydrophobic character (it has a calculated log P of >6.5, so should be enriched >1 million fold in the membrane plane). In short, oleamide is made in membranes and degraded there. We can see no reason for it to be secreted from the membrane in large amounts (although we are engaged in experiments to address this issue) and certainly not to equilibrate between bulk CSF and localized sites of action (presumably hypothalamic and brain stem sleep centres). Because of the close analogies with anaesthetics in terms of its *in vitro* profile at crucial neural ion channels we believe that endogenous lipids of this nature should seriously be considered as endogenous ligands for recognition sites exploited by clinically important depressant drugs.

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CLINICAL INVESTIGATIONS

Predictive factors of early morphine requirements in the post-anaesthesia care unit (PACU)

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Use of morphine by titration in the post-anaesthesia care unit (PACU) is often the first step in postoperative pain management. This approach provides rapid analgesia but shows a wide inter-individual variability in morphine requirements and may prolong patient stay in the PACU. The aim of this study was to identify the patient characteristics, surgical, anaesthetic, and post-operative factors predictive of early morphine requirements. The study included 149 patients undergoing various non-cardiac surgical procedures under general anaesthesia. In the multiple regression analysis of nine variables, only ethnicity (Caucasian), emergency surgery, major surgery, surgery exceeding 100 min, and pain score on arrival in PACU were predictive factors of morphine requirements. This observational study identifies for the first time independent predictive factors of morphine requirements in the early postoperative period. Future studies are warranted to evaluate the impact of intervention on these factors and any resulting improvement in postoperative pain treatment.

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The management of acute pain has undoubtedly improved over the last few years. There is now increased interest in it, and effective pain relief after surgery is an essential element of good postoperative management.

In the post-anaesthesia care unit (PACU), the use of titrated doses of morphine is often the first step in postoperative pain treatment. Morphine by titration requires initial assessment of the pain but provides rapid analgesia and the ability to adapt the dose to individual requirements.[1 2] Although in common use, there are several limitations of this approach. Intravenous (i.v.) administration of boluses of morphine needs regular pain and sedation assessment. Such management is time consuming for nurses, prolongs patient stay,[3] and contributes to the increased cost of PACU admission. There is also wide inter-individual variability in opioid requirements.[4 5] Contrary to the later postoperative period (24 h plus) where correlation between physical characteristics, psychological factors, and opioid requirements has been reported,[6–8] there has been little evaluation of the factors that contribute to variations in morphine requirement in the early postoperative period.

The aim of this study was to identify the patient characteristics, surgical, anaesthetic, and postoperative factors that contribute to variability in early postoperative morphine requirements.

Methods

Study site

This prospective study was carried out during a 2-week period in a university hospital. This hospital has 402 surgical beds and admits on average 12 600 surgical patients each year. All surgical procedures except cardiac surgery (i.e. orthopaedic, general, urological, gynaecological, and ear, nose and throat) were included in the study.

Patients

All in-patients (including for emergency procedures) undergoing surgery under general anaesthesia, were included in the study. Patients underwent routine pre-operative assessment and were informed about postoperative pain manage-

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Table 1 Types of operation classified as major, intermediate, and minor procedures according to the expected level of postoperative pain[9,10]

Major	Intermediate	Minor
Gastrectomy	Appendicectomy	Minor urological procedures (transurethral prostatectomy, testicular surgery)
Splenectomy	Laparoscopic procedures	Circumcision
Liver/pancreatic surgery	Mastectomy	Superficial surgery
Oesophageal surgery	Inguinal hernia	Examination under anaesthesia/anal fissure repair/anal stetch
Laparotomy/bowel resection	Vaginal/hysterectomy	Varicose veins
Laparotomy/cholecystectomy	Thyroidectomy	
Laparotomy/hysterectomy	Ear, nose and throat surgery (other than adenoidectomy)	
Haemorrhoidectomy	Total hip replacement	
Thoracic surgery		
Spinal fusion		
Renal surgery		
Total knee replacement or arthrolysis		
Adenoidectomy		

ment. Patients having any one of the following criteria were excluded: regional block, epidural or spinal anaesthesia or analgesia, inability to read or speak French, the likelihood of delayed postoperative tracheal extubation in the PACU, ASA physical status over 3, or incomplete records.

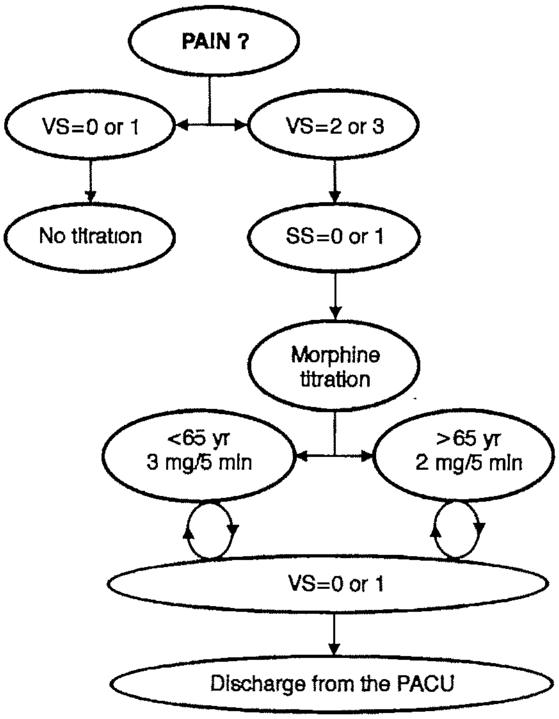

Fig 1 Standard procedure for morphine titration in PACU. Pain assessment with the verbal score (VS): ask the patient 'Which of the following words best describes the pain you are experiencing at the moment': none=0, mild pain=1, moderate pain=2, severe pain=3. Sedation score (SS): look at the patient and decide which of the following apply: awake=0, dozing intermittently=1, mostly sleeping=2, only awakens when aroused=3.

Study design

We performed an observational study and patients were included consecutively as they presented. During the study period, the anaesthetic and postoperative pain management did not vary from routine practice; hence, ethics committee approval and informed consent were not needed. We prospectively collected the physical characteristics, surgical, anaesthetic, and postoperative data of each patient. A data sheet was kept postoperatively (from day 1) for each patient by the PACU resident. Operations were grouped as major, intermediate, or minor procedures according to the expected level of postoperative pain as proposed by Gould and the French Society of Anaesthesiology (Table 1).[9,10]

In the PACU after surgery, patients complaining of pain were given i.v. bolus doses of morphine that were repeated until the patient felt comfortable. Pain intensity level was assessed using a verbal score (VS) (Fig. 1). Morphine boluses were given by the nurse using the standardized procedure currently used in our hospital (Fig. 1). The procedure sets no limit to the total dose that can be given in the absence of excessive sedation or hypotension.

For patients who did not require morphine titration because of low pain intensity (VS $\leq$1), postoperative analgesia was achieved with i.v. propacetamol. Patients were not discharged from the recovery room until they were comfortable with a VS $\leq$1.

Statistical analysis

Data were categorized as shown in Table 2. In the analysis, all factors have been considered as binary variables: age ($\leq$65 yr=1, >65 yr=2); sex (female=1, male=2); ethnicity (African and Asian people=1, Caucasian=2); type of surgery (major=1, intermediate and minor=2); context of surgery (scheduled=1, emergency=2); duration of surgery ($\leq$100 min=1, >100 min =2); surgeon grade (senior=1, junior=2); type of intra-operative opioid (none or alfentanil=1, fentanyl or sufentanil=2); total dose of intra-operative opioid (low=1, high=2); intra-operative administration of non-opioid analgesic (none=1, propacetamol, nefopam or ketoprofen=2); time between last injection of opioid and arrival in the PACU (low=1, high=2); sedation score on arrival in the PACU (0 or 1=1, 2 or 3=2); and pain score on arrival in the PACU (0 or 1=1, 2 or 3=2). For each variable, the total corresponding morphine dose (mg) is

Table 2 Data categorization used for statistical analysis. *For the duration of surgery and the dose of intra-operative opioid, the categorization is determined by the mean value of each variable. Patients received any one of the three opioids. §For the time between last injection of opioid and arrival in PACU, the categorization into low or high is based on the duration of analgesic effect of each opioid

Variable	Low	High
Duration of surgery* (min)	≤100	>100
Dose of intra-operative opioid*	Fentanyl ≤250 μg Sufentanil ≤30 μg Alfentanil ≤1000 μg	Fentanyl >250 μg Sufentanil >30 μg Alfentanil >1000 μg
Time between last injection of opioid and arrival in PACU§ (min)	Fentanyl ≤60 Sufentanil ≤45 Alfentanil ≤30	Fentanyl >60 Sufentanil >45 Alfentanil >30

expressed as mean (SD) with 95% confidence intervals. For all variables, an appropriate test has been performed to ensure the data is normally distributed. For small subgroups (below 30 patients each) we used a graphical technique. The total dose of morphine required for pain relief was compared between groups using analysis of variance (ANOVA).

To identify predictive factors of morphine consumption, variables that were found significant using ANOVA were included in a stepwise, backward, multivariate analysis model. The multiple regression analysis (MRA) model used was: $Y=B+B_1X_1+B_2X_2+B_3X_3+\ \dots\ B_nX_n$, where Y is the dependent variable (total morphine dose titrated) and $X_{1,2,3}\dots$ the independent variables.

A P value of <0.05 was considered statistically significant. All statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 9.0 for Windows 95/98.

Results

Patient characteristics

During the study period, 205 patients underwent a surgical procedure under general anaesthesia and 149 patients fulfilled the criteria for inclusion in the analysis. Fifty-six patients were subsequently excluded from the study because of: delayed extubation (13 patients); ASA physical status over 3 (eight patients); inability to read or speak French (15 patients); and incomplete data records (20 patients). The characteristics of the study population are shown in Table 3.

Univariate analysis

Factors for which a significant difference in the total dose of morphine was found were: sex, ethnicity, type, context and duration of surgery, type and amount of intra-operative opioids, time between last injection of opioid and arrival in the PACU, and finally, postoperative pain on arrival in the PACU. In contrast, there was no significant difference for age, surgeon grade, intra-operative administration of non-opioid analgesics such as propacetamol, nefopam or ketoprofen, and sedation score at the arrival in the PACU (Table 3).

Table 3 Morphine requirements for pain relief in the PACU

	n	Morphine (mg) (mean (SD))	95% confidence interval of mean (mg)	*P* value
Age				
≤65 yr	114	3 (5)	2–4	NS
>65 yr	35	3 (5)	2–5	
Sex				
Male	93	2 (4)	3–5	<0.001
Female	56	3 (3)	1–5	
Ethnic group				
Caucasian	93	5 (6)	3–5	<0.001
Others (African, Asian)	56	1 (3)	1–2	
Type of surgery				
Major	49	4 (5)	3–5	<0.001
Intermediate/minor	100	1 (3)	0–2	
Scheduled	127	3 (4)	2–4	<0.05
Emergency	22	5 (6)	2–8	
Duration of surgery				
≤100 min	91	2 (4)	1–3	<0.001
>100 min	58	5 (5)	4–7	
Surgeon grade				
Senior	89	3 (5)	2–3	NS
Assistant	60	3 (4)	3–6	
Type of opioid used				
None/alfentanil	63	4 (5)	3–6	0.001
Fentanyl/sufentanil	86	1 (4)	0–2	
Intra-operative opioid dose				
Low	85	4 (6)	3–6	0.01
High	64	2 (4)	1–3	
Non-opioid analgesic				
None	85	3 (5)	2–4	NS
Propacetamol/ nefopam/ketoprofen	64	4 (5)	2–5	
Time between last injection of opioid and arrival in PACU				
Low	70	2 (4)	1–3	<0.05
High	79	6 (6)	3–6	
Sedation score				
0 or 1	117	3 (5)	2–4	NS
2 or 3	32	3 (4)	1–4	
Pain score (verbal score)				
0 or 1	102	1 (3)	1–2	<0.001
2 or 3	47	6 (6)	5–8	

Multiple regression

Independent predictive factors of morphine requirements were: context of surgery (emergency), duration (>100 min), pain score on arrival in the PACU (2 or 3), ethnicity (Caucasian), and type of surgery (major) with a $R^2=0.38$. The equation for the regression model was: $Y=2.3$ (emergency surgery)+1.9 (duration of surgery >100 min)+1.6 (pain score on arrival in PACU at 2 or 3)+1.6 (Caucasian ethnicity)+0.9 (major surgery)−1.36. Sex, type, and amount of intra-operative opioid, and time between last injection of opioid and arrival in PACU were not found to be independent predictive factors of morphine requirements (Table 4).

Discussion

This prospective, observational study suggests that ethnicity, type, context and duration of surgery, and initial

Table 4 Independent predictive factors of morphine requirements in the PACU from the multiple regression analysis

Variable	Odds ratio	95% Confidence interval	*P* value
Context of surgery (emergency)	9.5	1.3–67	0.02
Duration of surgery (>100 min)	7	1.5–33	0.01
Pain score on arrival in PACU (2 or 3)	5	2.6–10	0.0001
Ethnicity (Caucasian)	5	1.1–22.7	0.03
Type of surgery (major)	2.4	1.1–5.8	0.04

postoperative pain score are predictive factors of morphine requirements in the PACU after general anaesthesia.

However, some methodological limitations have to be considered. First, this study included only a restricted sample of 149 patients. This may have decreased the power of the study, particularly for the negative findings, which were significant in the univariate analysis but not in the multiple regression analysis. Second, there is a possibility of confounders among the factors identified as significant in the univariate analysis. However, multiple regression analysis looks at the independency of these factors thereby ruling out those considered as possible confounders. Third, the value of R^2 in the multiple regression was 0.38. This means that 38% of the variability in the morphine requirements was explained by variability in the factors analysed. That leaves 62% of the variability that is not explained by any of the measured variables. Factors not considered in this study have to be taken into account. For example, psychological factors may be responsible for some of the inter-patient variability.[11–13] In our study, an increased anxiety level could probably explain the finding that emergency surgery is a predictive factor of morphine requirements. Patients operated on as an emergency are more anxious because they receive less information and do not benefit from any anxiolytic pre-medication. Because of these methodological considerations, this study can only be considered as preliminary work.

The positive findings in this study are not exactly the same as those reported for the later postoperative period (24 h plus). Ethnicity appears as a predictive factor of morphine consumption. Caucasian people required more morphine than Africans and Asians. It could be argued that this result is related to a higher incidence of Caucasian people in our study. However, the expression of pain and analgesic requirements has been shown to differ in various ethnic groups.[14–17] In addition, Uhl and colleagues[18] have demonstrated that a major source of variability in pain sensation and response to opioids is genetic. Alternatively, our finding could be explained by a higher socioeconomic status and level of formal education in Caucasian people in our institution.[19] It cannot be excluded that the predictive value of ethnicity could be related to other variables such as alcohol intake with hepatic enzyme induction, as increased requirements for intra-operative opioid have been reported in chronic alcoholics.[20]

As with previous observations,[21 22] we found a significant influence of surgical factors on morphine requirements. An original finding was that surgery exceeding 100 min duration was associated with increased morphine requirements. Pain score on arrival in PACU (moderate or severe) was also a predictive factor of morphine requirements. This is in agreement with previous work that reported an increase in postoperative opioid requirements with increased post-operative pain levels.[23] It could be argued that this result was to be expected as the procedure for morphine titration was based on pain scores. Nevertheless, the sedation score also used in the procedure did not appear as a predictive factor of morphine requirements.

In contrast, some variables previously reported to predict postoperative opioid requirements had no significant influence on morphine consumption in the PACU in our study. Increasing age has been found to decrease opioid requirements in numerous studies.[6–8 24] However, we failed to show a significant influence of age on early morphine requirements. This result could be related to the procedure used because it took into account the age of the patients (boluses of 3 mg under 65 yr and 2 mg over 65 yr, Fig. 1). Nor was our procedure weight related because it has been demonstrated that morphine requirements are better correlated to the age than the weight of the patient.[7] Procedures of morphine titration only based on age are used in other institutions.[25] Sex also did not appear as a predictive factor of morphine consumption in the PACU. This result is consistent with a clinical study in volunteers that has failed to find an effect of sex on morphine-induced behavioural and physiological responses.[26]

For the later postoperative period, previous results are conflicting. Macintyre and Jarvis[7] noted that male gender was a predictive factor of postoperative PCA morphine requirements although in their study, age was the best predictive factor. In contrast, other authors have reported a greater need for pain relief in women.[27]

Surprisingly, the type of anaesthetic, the amount of opioid used intra-operatively, and the time of the last injection of opioid, although significantly related to morphine consumption in the univariate analysis, were not independent predictive factors in the multiple regression analysis. This discrepancy could be related to the fact that these variables are probably dependent on the type of surgery performed and could be considered as confounding factors. An important finding of this study is the lack of significant association between intra-operative administration of propacetamol, ketoprofen or nefopam, and morphine requirements. These analgesics were usually administered between 30 and 60 min before the end of surgery in anticipation of postoperative pain. Although these results do not support the use of non-opioid analgesics, further work is required because of the lack of power of our study.

How can the identification of these predictive factors improve postoperative pain management? Few of these variables are accessible to medical intervention. However, reduction of pain intensity on arrival in the PACU can be considered a reasonable goal. This can be achieved by the use of regional analgesia when possible.[28–30] The concept of pre-emptive analgesia has been also suggested.[31] Although pre-emptive analgesia is an attractive working hypothesis, the results appear conflicting in the literature.[32–34] Other approaches such as intra-operative titration of morphine could be investigated further. This technique decreases postoperative pain scores, morphine requirements, and patient length of stay in the PACU.[25]

In conclusion, this study opens up areas for further investigation of pain management in the early postoperative period. It is of importance because this period has clinical and economic implications.

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Hormonal and metabolic stress responses after major surgery in children aged 0–3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine[†]

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Children aged 0–3 yr were stratified for age and randomized to receive either continuous morphine (CM, 10 μg kg^{-1} h^{-1}) with three-hourly placebo boluses or intermittent morphine (IM, 30 μg kg^{-1} every 3 h) with a placebo infusion for postoperative analgesia. Plasma concentrations of epinephrine, norepinephrine, insulin, glucose and lactate were measured before and at the end of surgery and 6, 12 and 24 h after surgery. Pain was assessed with validated pain scales [the COMFORT scale and a visual analogue scale (VAS)] with the availability of additional morphine doses. Minor differences occurred between the randomized treatment groups, the oldest IM group (aged 1–3 yr) having a higher blood glucose concentration (P=0.003), mean arterial pressure (P=0.02) and COMFORT score (P=0.02) than the CM group. In the neonates, preoperative plasma concentrations of norepinephrine (P=0.01) and lactate (P<0.001) were significantly higher, while the postoperative plasma concentrations of epinephrine were significantly lower (P<0.001) and plasma concentrations of insulin significantly higher (P<0.005) than in the older age groups. Postoperative pain scores (P<0.003) and morphine consumption (P<0.001) were significantly lower in the neonates than in the older age groups. Our results show that continuous infusion of morphine does not provide any major advantages over intermittent morphine boluses for postoperative analgesia in neonates and infants.

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In adults, endocrine and metabolic responses to severe injury consist of a hypometabolic period, which lasts about 3 days, followed by a hypermetabolic period.[1 2] As a result of this homeostatic disturbance, cellular dehydration, capillary leakage and organ dysfunction may occur, leading to a prolonged convalescence period.[3] Although this endocrine-metabolic response can be modified by surgical anaesthesia, important reductions in stress responses depend on the analgesic method in adult patients[4 5 6] and in children.[7] Epidural anaesthesia was more effective in reducing surgical stress during low abdominal surgery than systemic opioids.[8] Diminished stress responses and improved postoperative outcomes were noted after high-dose opioids in neonates after cardiac surgery.[9 10] More recently, the use of i.v. opioids in non-surgical, mechanically ventilated neonates resulted in reduced physiological and behavioural measurements of pain and stress[11 12] and was associated with fewer periods of hypoxaemia[13] and

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improved neurological outcomes.[14] Because of the lack of randomized controlled trials in neonates and infants,[15] little is known about the alterations in hormonal-metabolic stress responses caused by postoperative analgesia or postnatal age in patients undergoing non-cardiac surgery.

This study was designed as a double-blind, randomized controlled trial to test the hypothesis that postoperative analgesia with continuous morphine infusion would provide improved analgesia with lower stress responses compared with intermittent doses. To obtain more information about physiological and behavioural responses after major surgery in young children, surgical stress was evaluated by measuring hormonal, metabolic and haemodynamic variables and postoperative pain was assessed by behavioural responses [COMFORT and a visual analogue scale (VAS)] and by the amount of morphine used. The ontogeny of these responses is unknown because of the paucity of data beyond the neonatal age group. Therefore, we randomized the patients into four developmentally relevant age groups.[16]

Methods

The study protocol was approved by the hospital medical ethics committee, and written consent was obtained from the parents. We included children aged 0–3 yr, admitted to the paediatric surgical intensive care unit (PICU) after non-cardiac thoracic and abdominal surgery. Patients were excluded if they had received analgesic or sedative drugs <6 h before surgery, if they were receiving neuromuscular blockade or if they suffered from hepatic, renal or neurological disorders or altered muscle tone. Patients were stratified by age into four groups [group I, 0–4 weeks (neonates); group II, 4 weeks to 6 months; group III, 6–12 months; group IV, 1–3 yr] and were assigned randomly to receive i.v. either continuous morphine (CM) or intermittent morphine (IM). The pharmacists prepared all study drugs, and the strata-specific schedules for randomization and the clinical staff were blinded to the study group allocation until data collection was complete.

Anaesthetic management was standardized. Anaesthesia was induced i.v. with thiopentone 3–5 mg kg^{-1} or by inhalation of halothane in oxygen. Fentanyl 5 µg kg^{-1} was given before orotracheal intubation, which was facilitated with atracurium 0.5–1 mg kg^{-1} or suxamethonium 2 mg kg^{-1}. Ventilation was controlled and anaesthesia was maintained with isoflurane 0.5 minimum alveolar concentration in 60% nitrous oxide in oxygen or air in oxygen. Perioperative fluids were standardized to maintain a glucose infusion rate between 4–6 mg kg^{-1} min^{-1}. Body temperature was kept within normal ranges. A peripheral artery was cannulated and the measured mean arterial blood pressure (MAP) and heart rate (HR) were used as preoperative baseline data. After the first arterial blood sample (baseline), patients received a second dose of fentanyl 5 µg kg^{-1} before surgical incision. Additional doses of fentanyl 2 µg kg^{-1} were administered when HR and/or MAP were 15% above baseline value. At the end of surgery, the neuromuscular block was antagonized and the tracheal tube was removed. Mechanical ventilation was continued in patients who required ventilatory assistance after surgery.

Directly after surgery, all patients received an i.v. loading dose of morphine (100 µg kg^{-1}) followed by a morphine infusion of 10 µg kg^{-1} h^{-1} for children in the CM group, combined with three-hourly i.v. placebo (saline) boluses. Children in the IM group received a continuous placebo infusion (saline) combined with three-hourly i.v. doses of 30 µg kg^{-1}. The first intermittent bolus (morphine or placebo) was given 3 h after surgery. Additional analgesia was given by the nurse when there were signs of pain, indicated by a VAS score ≥4. During the first hour after surgery, one-third of the loading dose of morphine could be repeated every 15 min, and thereafter morphine 5 µg kg^{-1} could be given every 10 min if required. No other analgesic or sedative drugs were used.

Arterial blood samples were taken after induction of anaesthesia, at the end of surgery and 6, 12 and 24 h after surgery to determine plasma concentrations of epinephrine, norepinephrine, insulin, glucose and lactate. From 24 to 36 h after surgery, urine was collected for determination of the 3-methyl histidine/creatinine molar ratio (3MH/CR), a measure of protein breakdown.

After surgery, the Surgical Stress Score (SSS)[17] was computed by the surgeon and anaesthetist. Nurses performed regular assessments before surgery (baseline) and every 3 h up to 36 h after surgery. Nursing interventions included pain assessment using a VAS and the COMFORT scale,[18] blood sampling (as indicated), giving the intermittent bolus (placebo or morphine), and then nursing as needed. Thus, hormonal and metabolic stress responses were measured as plasma concentrations at time points corresponding to trough plasma morphine concentrations in the IM group.

The SSS consists of seven items: amount of blood loss; site of surgery; amount of superficial trauma; extent of visceral trauma; duration of surgery; associated stress factors (hypothermia, localized or generalized infection and prematurity); and cardiac surgery.[17] The total scores in this study (excluding cardiac surgery and prematurity <35 weeks) ranged from 3 to 24, and were used to classify the degree of surgical stress.

The VAS, a horizontal continuous 10 cm line with the anchor points 'no pain' on the left and 'extreme pain' on the right, was used as an observational instrument. VAS scores <4 indicate absent or mild pain and scores ≥4 indicate moderate to severe pain, as noted from previous studies in children.

The COMFORT scale[18 19] was originally developed and validated to assess distress in children ventilated mechanically (0–18 yr). This scale consists of six behavioural items (alertness, calmness, respiratory response, movement, muscle tone and facial expression) and two physiological items (MAP and HR). For non-ventilated children, the respiratory response item was replaced by an assessment of crying, possible scores ranging from 1 (no crying) to 5 (screaming). Total score ranges from 8 to 40. We have recently validated the COMFORT scale as a measure of postoperative pain in this age group.[20]

Plasma concentrations of epinephrine and norepinephrine were measured by HPLC using fluorimetric detection.[21] Plasma concentrations of insulin were measured using the Insulin IRMA CT kit (Medgenix). Standardized automated laboratory analysers measured plasma concentrations of glucose, lactate, total bilirubin and plasma and urinary creatinine. The concentration of urinary 3-methylhistidine was measured by ion exchange chromatography on an amino acid analyser.

In previous studies, a SD of 0.6 nmol litre^{-1} was found for epinephrine and 1.4 nmol litre^{-1} for norepinephrine.[10] To detect differences between the group values for plasma epinephrine (0.24 nmol litre^{-1}) and norepinephrine (0.56 nmol litre^{-1}) with a power of 80% at a two-sided alpha error of 0.05 would require 100 patients in each group. Repeated measurements analysis of variance (RmANOVA)[22] was used to evaluate simultaneously the effects of treatment, age groups and time after surgery. Plasma concentrations before surgery and changes from baseline values directly after surgery were compared between age groups using one-way ANOVA. Comparison with baseline values within age groups was by the paired *t*-test. In these analyses, all hormonal and metabolic data had to be transformed logarithmically in order to obtain approximately normal distributions. The postoperative time points (directly after surgery and 6, 12 and 24 h after surgery) at which individual plasma concentrations were highest were compared between age groups using the Kruskal–Wallis/Mann–Whitney test. The same tests were used to compare morphine consumption between groups. Correlation coefficients given are Spearman's.

All enrolled patients were included in an intention-to-treat analysis. Nine patients dropped out during the study (five in CM, four in IM) because of the loss of arterial access (seven), the need for neuromuscular blockade (one) and one postoperative death 3 h after surgery.

Results

Table 1 shows the clinical and surgical characteristics of the enrolled patients according to their age categories and randomized treatment groups.

A total of 204 patients were enrolled: 101 in the CM group and 103 in the IM group. The randomization schedule was stratified for age; other demographic and clinical variables were similar in the two randomized groups. Thirteen of the 35 neonates in the CM group (37%) were ventilated mechanically before surgery compared with six of the 33 in the IM group (18%). This difference was not significant.

For various reasons, 23 patients needed mechanical ventilation before surgery, seven of them for acute inflammatory surgical complications.

The median doses of fentanyl for age groups I, II, III and IV were 12, 12, 17 and 15 µg kg^{-1} respectively. Fentanyl doses did not differ significantly between the two treatment groups in any of the age groups (all $P>0.14$). The fentanyl dose correlated significantly with the duration of surgery ($r=0.43$, $P<0.001$). The age groups were similar with respect to SSS.

Hormonal and metabolic stress responses

Table 2 shows the median and interquartile range of the hormonal and metabolic variables before and after surgery (average of 6, 12 and 24 h after surgery) according to age and treatment.

Overall, no significant differences in plasma concentrations were found between the randomized treatment groups (all analyses $P\geqslant0.22$). For glucose, a significant interaction was found between the effects of treatment and age ($P=0.04$), indicating that the treatment difference was not the same in all age groups. Further analysis within each age group showed that blood glucose concentrations were lower in the CM group (16%, $P=0.003$) than in the IM group in the oldest age group (1–3 yr), although an opposite trend was noted among the neonates (CM>IM, $P=0.07$).

Figure 1 shows the geometric mean plasma concentrations with the SE for epinephrine, norepinephrine, insulin, glucose and lactate and the insulin/glucose ratio, for all patients, according to age, at the various time points (before and at the end of surgery and 6, 12 and 24 h after surgery).

Plasma concentrations of epinephrine before surgery were not significantly different between the age groups. The mean increase in plasma epinephrine concentration directly after surgery was significantly lower in the neonatal group than in the other age groups (1.6 *vs* 6–8 times baseline value, $P<0.001$), and no significant differences occurred between the older age groups. Mean values of the average postoperative plasma concentration of epinephrine (6, 12 and 24 h after surgery) were significantly lower in the neonatal group than in the older children (all $P<0.001$). RmANOVA showed that postoperative decreases in plasma epinephrine differed significantly between the age groups ($P<0.001$). In the neonates, the mean plasma concentration of epinephrine had returned to the baseline value 6 h after surgery and was below the baseline value at later time points ($P<0.05$). In the older age groups, mean values were still above baseline 24 h after surgery (all $P<0.001$). The highest plasma concentrations were mostly found directly after surgery in age groups I and III, and 6 h after surgery in age groups II and IV. Plasma epinephrine concentrations were not significantly different with respect to spontaneous or mechanical ventilation.

Plasma norepinephrine concentrations at baseline were significantly higher in the neonates than in age group II ($P=0.01$) and nearly so in comparison with age groups III

Table 1 Patient data [mean (range or SD)] and details of surgery. CM=continuous morphine, IM=intermittent morphine; n=number of patients. High abdominal surgery comprised diaphragmatic hernia/paresis, duodenal atresia, subtotal pancreatectomy, Nissen fundoplication, hepatic and choledochal surgery, (ad)renal surgery, stomic perforation. Superficial surgery comprised nephrectomy, ureter reimplantation, pyeloplasty, and operations for exstrophy of the bladder, sacroteratoma, yolk sac tumour, pull-through, incarcerated hernia. Acute gastrointestinal surgery comprised operations for atresia, malrotation, intussusception, necrotizing enterocolitis, meconium peritonitis and perforation, and ileus surgery

	Age group							
	I (0–4 weeks)		**II (4–26 weeks)**		**III (26–52 weeks)**		**IV (1–3 yr)**	
	CM (n=35)	**IM** (n=33)	**CM** (n=34)	**IM** (n=33)	**CM** (n=16)	**IM** (n=15)	**CM** (n=18)	**IM** (n=22)
Age (days)	8	3	97	101	267	254	632	639
(range)	(0–28)	(0–17)	(29–173)	(30–179)	(185–351)	(180–330)	(368–1070)	(393–1067)
Weight (kg)	3.1 (0.7)	2.9 (0.5)	4.9 (1.5)	4.6 (1.8)	6.9 (1.6)	7.3 (1.2)	11.1 (1.9)	11.1 (2.5)
Males/females (n)	21/14	19/14	21/13	22/11	9/7	9/6	9/9	10/12
Mechanical ventilation before surgery	13	6	4					
Total Surgical Stress Score	9.9 (2.8)	9.9 (2.9)	9.3 (3.3)	9.6 (2.5)	8.4 (3.1)	9.9 (2.7)	10.6 (2.9)	10.1 (3.7)
Generalized or localized infection	5	6		1			1	1
Surgical procedures								
Congenital diaphragmatic hernia	9	4			1	1		1
Tracheo-oesophageal atresia/TOF	6	9	1	1				
Bronchopulmonary (lobectomy, pneumectomy, cyst)		1	2	1			1	5
Cardiac (Blalock, vessel loop)			1	2				
Nissen fundoplication				2	2	2	2	4
Gastroschisis	1	1						
Acute gastrointestinal	15	15	11	5	5	2	3	2
Colonic pull-through					1			2
Closure of entero/colostoma			7	9	1	3	1	4
Rehbein's procedure	1		4	4	1	3		
Colon interposition							3	1
Urological (nephrectomy, pyeloplasty, reimplantation, bladder augmentation)		1	1	2			1	2
Miscellaneous (diaphragma paresis, tumour, teratoma, cyst, pancreatectomy, choledochal atresia)	1	2	7	7	5	3	2	7
Site of surgery								
Thoracic	5	8	6	4		2	5	1
Abdominal high/low	16/12	6/17	7/20	8/19	8/7	3/10	6/3	5/11
Thoracic combined with abdominal		2					3	2
Superficial			1	2	1		1	3

and IV (both P=0.06). The increases in plasma norepinephrine concentrations (6, 12 and 24 h after surgery) compared with baseline values were significantly smaller in the neonates than in age groups II (P=0.004) and III (P=0.05). The mean average plasma concentration of norepinephrine (6, 12 and 24 h after surgery) showed no significant differences between age groups or assessment times. Only for the oldest age group was there a significant increase in plasma concentrations 6 h after surgery (P=0.03). No significant differences were found between age groups regarding the time at which individual patients reached the highest plasma concentration. In all age groups, plasma concentrations of norepinephrine were still significantly above baseline values 24 h after surgery (all P<0.001). Neonates who were ventilated mechanically showed significantly higher plasma concentrations of norepinephrine before operation compared with the non-ventilated neonates (P=0.02). This difference was not significant in the postoperative period. In patients of age group II (1–6 months) needing mechanical ventilation after surgery, there were significantly higher plasma concentrations of norepinephrine compared with the non-ventilated children of that age group (P=0.02).

Plasma insulin concentrations at baseline were not significantly different between the age groups; however, directly after surgery, plasma concentrations were significantly higher in the neonates than in age groups III (P=0.002) and IV (P<0.001). The average plasma concentration of insulin (6, 12 and 24 h after surgery) showed a significant correlation with age (r=–0.34, P<0.001).

Plasma glucose concentrations before surgery were not significantly different between the age groups and they were generally highest directly after surgery in all age groups. RmANOVA of glucose plasma concentrations 6, 12 and 24 h after surgery showed a significant decrease after surgery (P<0.001). At 24 h after surgery, mean plasma concentrations were not significantly different from baseline values in all age groups.

Table 2 Hormonal and metabolic variables before and after surgery (average of 6, 12 and 24 h after surgery) according to age and treatment All values are median (interquartile range). CM=continuous morphine; IM=intermittent morphine; *n*=number of patients

	Age group															
	I (neonates, 0–4 weeks)				**II (4 weeks to 6 months)**				**III (6 months to 1 yr)**				**IV (1–3 yr)**			
	CM	*n*	IM	*n*	CM	*n*	IM	*n*	CM	*n*	IM	*n*	CM	*n*	IM	*n*
Epinephrine (nmol litre^{-1})																
Before surgery	0.1 (0.03–0.36)	34	0.11 (0.04–0.33)	32	0.07 (0.02–0.2)	29	0.10 (0.05–0.22)	32	0.11 (0.05–0.34)	16	0.16 (0.08–0.37)	15	0.19 (0.04–0.29)	18	0.10 (0.05–0.65)	21
After surgery	0.14 (0.05–0.28)	33	0.06 (0.03–0.29)	30	0.56 (0.31–0.97)	27	0.57 (0.36–0.97)	26	1.02 (0.6–1.81)	15	1.05 (0.67–1.67)	14	1.42 (0.94–2.02)	15	1.93 (1.43–2.55)	17
Norepinephrine (nmol litre^{-1})																
Before surgery	1.6 (98–3.2)	34	1.6 (0.9–2.6)	32	1.1 (0.6-.9)	29	0.9 (0.6–1.8)	32	1.0 (0.6–1.9)	16	1.0 (0.7–1.8)	15	0.8 (0.5–1.5)	18	1.0 (0.4–2.3)	21
After surgery	2.6 (1.8–4.2)	33	2.1 (1.3–3.2)	30	2.7 (2.0–3.7)	27	2.6 (2.0–4.4)	26	2.6 (1.7–2.9)	15	2.6 (1.7–3.1)	14	2.4 (1.5–2.9)	15	2.3 (1.8–3.6)	17
Insulin (mU litre^{-1})																
Before surgery	5.0 (5.0–8.0)	31	5.0 (5.0–7.5)	29	5.0 (5.0–8.0)	31	5.0 (5.0–5.8)	32	5.0 (5.0–5.0)	16	5.0 (5.0–9.0)	15	5.0 (5.0–7.0)	18	5.0 (5.0–6.0)	22
After surgery	13.8 (9.4–17.1)	32	12.0 (8.5–19.6)	28	11.0 (8.7–14.3)	27	8.3 (6.0–12.2)	25	7.0 (5.7–11.3)	15	9.7 (7.5–12.6)	14	6.7 (5.3–10.0)	15	10.0 (6.8–12.8)	17
Glucose (mmol litre^{-1})																
Before surgery	5.5 (3.9–7.1)	35	5.7 (3.9–7.1)	32	5.8 (4.5–6.8)	31	5.6 (4.5–6.3)	32	4.5 (4.1–5.8)	16	5.6 (4.6–6.2)	15	4.5 (3.9–5.5)	18	4.9 (3.7–6.0)	22
After surgery	5.8 (5.2–6.7)	34	5.1 (4.5–6.7)	31	6.3 (5.1–6.5)	27	5.6 (5.1 –7.0)	25	5.8 (5.5–6.3)	15	6.3 (5.7–6.6)	14	5.9 (4.4–6.3)	15	6.7 (5.8–7.1)	18
Lactate (mmol litre^{-1})																
Before surgery	1.9 (1.3–2.7)	35	2.1 (1.3–2.8)	31	1.2 (1.0–1.4)	29	1.1 (0.8–1.3)	32	1.2 (0.9–1.5)	16	1.0 (0.9–1.5)	15	1.2 (0.8–1.5)	17	1.1 (0.8–1.3)	22
After surgery	1.5 (1.2–1.8)	32	1.5 (1.2–2.2)	29	1.2 (0.8–1.4)	25	1.0 (0.8–1.3)	24	0.9 (0.8–1.0)	15	0.8 (0.8–1.0)	14	0.9 (0.8–1.0)	15	0.9 (0.7–1.0)	17
Insulin/glucose ratio (U mol^{-1})																
Before surgery	1.1 (0.8–2.5)	31	1.1 (0.8–1.6)	28	1.1 (0.9–1.5)	31	1.0 (0.9–1.4)	32	1.2 (1.1–1.3)	16	1.1 (0.9–1.3)	15	1.2 (1.1–1.3)	18	1.1 (0.9–1.5)	22
After surgery	2.2 (1.8–3.0)	34	2.3 (1.7–3.1)	33	1.9 (1.6–2.5)	29	1.6 (1.1–2.0)	30	1.2 (1.0–2.1)	15	1.5 (1.3–2.1)	15	1.4 (1.1–1.7)	18	1.4 (1.0–1.9)	21

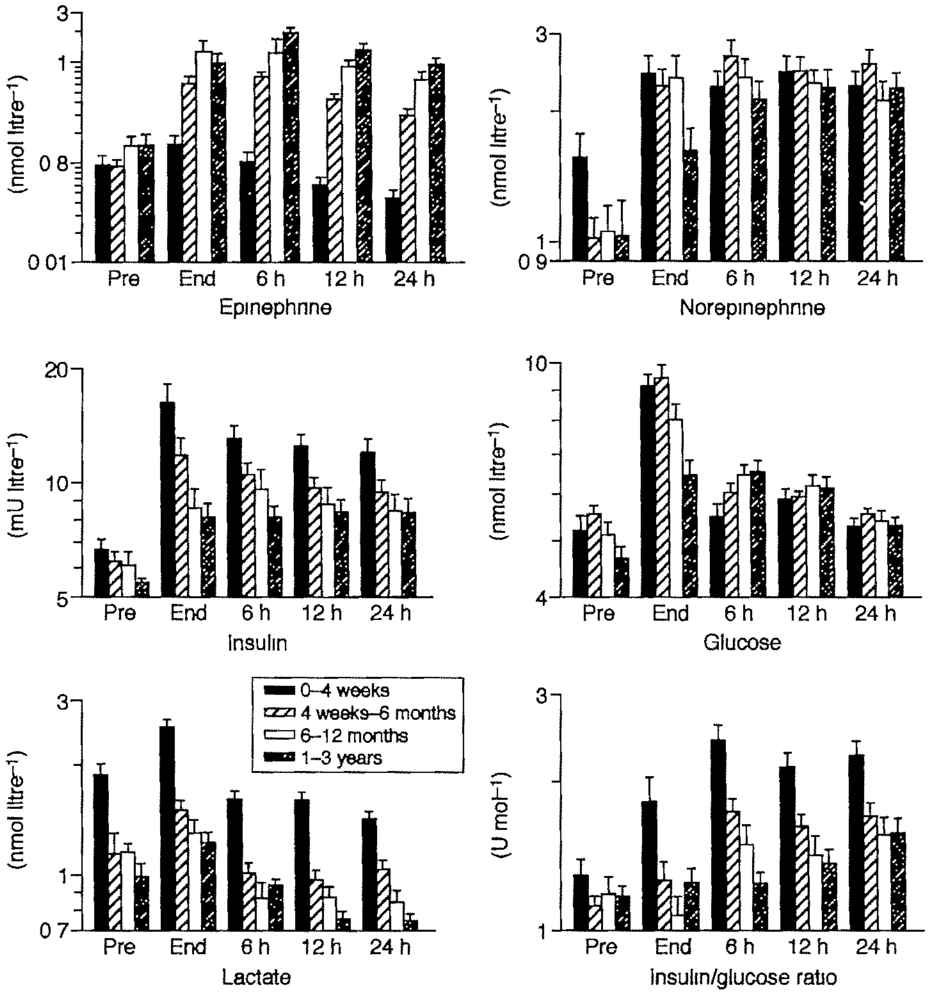

Fig 1 Plasma concentrations of epinephrine (nmol litre^{-1}), norepinephrine (nmol litre^{-1}), insulin (mU litre^{-1}), glucose (mmol litre^{-1}) and lactate (mmol litre^{-1}) and the insulin/glucose ratio (U mol^{-1}) The figure concentrates on the effects of age when the two treatment groups are combined. Data are geometric means with SE before surgery (Pre), at the end of surgery (End) and 6, 12 and 24 h after surgery Note the logarithmic scale of the vertical axes

The insulin/glucose ratio was not significantly different before operation, but showed significant differences after surgery between the age groups in their patterns of postoperative changes. There was a significant correlation ($r=-0.45$, $P<0.001$) between age and insulin/glucose ratio 6, 12, and 24 h after surgery. At 24 h after surgery, the mean insulin/glucose ratio was still above baseline for all age groups.

The mean plasma concentration of lactate at baseline was significantly higher in the neonates than in the other age groups (all $P<0.001$). Highest concentrations were found directly after surgery, with no significant difference in the change from baseline values between the age groups. In the neonatal group there was a significant decrease from 6 to 24 h after surgery ($P=0.02$). A similar effect was found in age group IV ($P<0.001$), but there were no significant postoperative differences for age groups II and III. Mean plasma concentrations of lactate were significantly below baseline values 24 h after surgery (all $P<0.001$). There was no significant difference in the urinary 3MH/Cr ratio (from 12 to 36 h after surgery) between the randomized treatment groups or the age groups.

Plasma concentrations of epinephrine ($P=0.01$) and norepinephrine ($P=0.003$) were significantly higher after upper abdominal surgery than after thoracic or superficial surgery. A repeated analysis that excluded the eight patients with 'superficial' surgery (Table 1) gave results similar to those in Table 3. In 14 patients (11 of them neonates), hormonal and metabolic stress responses may have been influenced by acute, inflammatory surgical complications. A repeated analysis that excluded the 14 patients with 'localized or generalized infection' again gave results similar to those in Table 3.

Significantly higher plasma concentrations of norepinephrine occurred after blood transfusion in neonates compared with neonates without transfusion at 6 ($P=0.01$), 12 ($P=0.07$) and 24 h ($P=0.03$) after surgery. These differences were not found in the other age groups.

Table 3 Comparison between continuous morphine (CM) and intermittent morphine (IM) by RmANOVA, while controlling for age group (I, II, III and IV), sampling time (6, 12 and 24 h after surgery) and preoperative (baseline) plasma concentration. Data are the ratio of geometric means (CM/IM). *Significant differences between the age groups: I, 1.12 (P=0.07); II, 0.99 (P=0.75); III, 0.96 (P=0.57), IV, 0.84 (P=0.003)

Variable	Ratio (CM/IM)	95% CL	*P*
Epinephrine	1.08	0.81–1.44	0.59
Norepinephrine	1.05	0.91–1.20	0.51
Insulin	0.92	0.81–1.05	0.22
Glucose	0.98*	0.95–1.04	0.52
Insulin/glucose ratio	0.97	0.86–1.08	0.55
Lactate	0.98	0.90–1.07	0.67

RmANOVA showed that postoperative increases in MAP (3–36 h after surgery) from baseline values depended on age. Significantly greater increases in the IM group compared with the CM group were found in age group III [12.0 (SD 5.8) mm Hg, P=0.04] and within age group IV [10.6 (4.4) mm Hg, P=0.02], but no significant differences were found in the other age groups.

In the neonates, mean HR at baseline was significantly higher in the CM than in the IM group (P=0.03). Increases in HR at the end of surgery or postoperatively were not significantly different between the two treatment groups. However, the change from baseline HR increased significantly with age (P=0.002), with maximum values recorded 6 h after surgery for all age groups.

Pain assessment

Postoperative pain scores, morphine consumption during the first 24 h after surgery and the number of patients needing postoperative mechanical ventilation during >36 h after surgery are shown in Table 4.

Mean VAS scores (3–36 h after surgery) were significantly different between the age groups but not between the CM and IM groups. VAS scores generally declined with time after surgery. More than 24 h after surgery, the mean VAS was still significantly higher in age group II than in each of the other age groups (all P<0.04).

The mean VAS scores were significantly lower in the neonates (1.3) than in the three older age groups (2.4, 2.1 and 1.8 respectively) (all P<0.003) and in group IV compared with group II (P<0.001). VAS scores of ≥4 occurred less frequently in neonates than in the older age groups (P<0.002) and in group IV compared with age group II (P=0.004). The occurrence of VAS ≥4 was correlated significantly with plasma concentrations of norepinephrine, but only in age groups III and IV at 6 h after surgery (both P<0.05).

The mean COMFORT score (3–36 h after surgery) was significantly different between CM and IM only in age group IV (18.8 and 20.8 respectively, P=0.02). Overall, the mean COMFORT score was significantly (P<0.001) lower in the neonates (17.4) than in the older age groups (21.4, 20.6 and 19.8 respectively). Generally, the plasma concentrations of epinephrine and norepinephrine were weakly correlated with COMFORT scores at the various time points.

Morphine consumption (excluding the loading dose) during the first 24 h after surgery was significantly different between the age groups, but not between the CM and IM groups. Morphine consumption during the first 24 h after surgery was significantly lower in the neonatal group than in age groups II, III and IV (all P<0.001), and significantly higher in group II than in group IV (P=0.035).

Discussion

We present the first randomized, placebo-controlled trial that includes a double-blind assessment of the clinical and physiological effects of continuous *vs* intermittent morphine for postoperative analgesia in neonates and older infants. In addition, we report important differences between the different age groups that will allow deeper understanding of the ontogeny of hormonal-metabolic stress responses in early life. Although the post-neonatal period is associated with major changes in the regulation of the hypothalamic-pituitary-adrenal axis and the hypothalamic sympathetic outflows (via the posterior hypothalamic nuclei and locus coeruleus), the effect of these developmental events on the neuroendocrine responses to surgical stress remains unclear.

On the basis of these data, we can reject our primary hypothesis that continuous infusions of morphine postoperatively produce improved postoperative analgesia and lower hormonal-metabolic responses. Although supplementary doses of morphine were used to treat clinical signs of distress after surgery, standard criteria were used for these treatments in the CM and IM groups. Clinical bias was eliminated by a double-blind study design and total morphine consumption was similar in the two randomized groups. The additional morphine doses were considered to be necessary for the patient's comfort and for ethical reasons. In infants aged 1–3 yr, greater degrees of stress were noted in the IM group than in the CM group, as noted by significant increases in postoperative hyperglycaemia, mean arterial pressure and clinical assessment by the COMFORT score. Because these measurements were performed at the time of trough morphine concentrations for the IM group, these differences may have been caused by the relatively great plasma clearance of morphine in this age group.[23–25] Thus, it is likely that the longer duration of opioid effect after intermittent morphine boluses in the younger age groups resulted in clinical and physiological effects that were similar to those of a continuous infusion.

Similar clinical trials in adult patients have reported conflicting results, suggesting superior[26], equivocal[27] or inferior[28] clinical effects of continuous i.v. infusions *vs* intermittent doses of morphine for postoperative analgesia. To our knowledge, a similar clinical trial has not been reported in paediatric patients, although several studies

Table 4 Postoperative pain scores [mean (SD)], morphine consumption in the first 24 h after surgery (excluding loading dose) [median (interquartile range)], and number of patients ventilated mechanically >36 h after surgery. The range of the visual analogue scale (VAS) is 1–10 and that of the COMFORT score is 3–24 *Average of values 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33 and 36 h after surgery CM=continuous morphine; IM=intermittent morphine, *n*=number of patients. Data are mean (SD)

	Age group															
	I (neonates, 0–4 weeks)				II (4 weeks to 6 months)				III (6 months to 1 yr)				IV (1–3 yr)			
	CM	*n*	IM	*n*	CM	*n*	IM	*n*	CM	*n*	IM	*n*	CM	*n*	IM	*n*
VAS score*	1.3 (0.8)	34	1.3 (0.5)	32	2.6 (0.8)	28	2.3 (0.9)	29	2.0 (0.8)	15	2.1 (0.8)	14	1.5 (1.2)	16	2.1 (1.2)	20
COMFORT score*	17.4 (2.9)	31	17.3 (2.3)	28	21.8 (2.0)	26	21.0 (3.1)	27	20.2 (3.1)	15	21.2 (3.1)	12	18.7 (3.1)	15	21.0 (2.6)	17
Morphine (μg kg^{-1} h^{-1})	10.0 (10.0–11.3)	34	10.0 (10.0–10.5)	33	12.3 (11.2–17.8)	29	11.6 (10.2–14.8)	30	11.7 (10.4–14.9)	15	12.1 (10.2–15.2)	15	10.9 (10.2–11.5)	17	11.0 (10.0–15.4)	21
Mechanical ventilation >36 h after surgery		26		15		4		7		0		1		2		2

comparing i.v. with epidural morphine analgesia have been reported.[29]

These data indicate that the pattern of surgical stress responses differs between neonates (postnatal age 0–4 weeks) and older age groups. Robust developmental differences were found for the postoperative changes in hormonal-metabolic variables (plasma epinephrine, norepinephrine, insulin and lactate), cardiovascular responses (MAP and HR), behavioural variables used for pain assessment (VAS and COMFORT scores), and postoperative morphine consumption.

Compared with previous data,[30] the magnitude of postoperative epinephrine responses was reduced in these neonates because of the effective anaesthetic and analgesic regimens used in the present study, although the brief duration of this response was similar to those in previous data.[30] Neonates with complex congenital heart defects were able to mount greater epinephrine responses,[10] suggesting that neonates are capable of increasing their production of epinephrine depending on the level of surgical stress. Decreased plasma concentrations of epinephrine at the end of surgery and decreased postoperative VAS and COMFORT scores in the neonates compared with older infants suggest that the doses used for fentanyl anaesthesia during surgery and postoperative morphine analgesia were inadequate for the older infants.[31] This is further corroborated by the greater amounts of additional postoperative morphine required by the older infants than by the neonates.

These findings can be explained by developmental differences in pharmacokinetic and pharmacodynamic factors between neonates and older infants. In studies comparing the effect of i.v. opioids (fentanyl at a mean dose of 1.3 μg kg^{-1} and morphine to a maximum of 0.2 mg kg^{-1}) with spinal and extradural analgesia during major surgery in infants (0–4 yr), all methods gave adequate postoperative analgesia, but more effective suppression of epinephrine and norepinephrine was found in the spinal and extradural groups.[8] In the present study, the mean plasma concentrations of epinephrine and norepinephrine were similar to those of the spinal and extradural groups, suggesting that the fentanyl doses were adequate even for high abdominal and thoracic surgery. Most full-term infants older than 4 weeks did not require mechanical ventilation, because they had opioid-induced ventilatory depression.

In contrast with the neonates, the older age groups had plasma concentrations of epinephrine that remained increased during the first 24 h after surgery, which might have been a result of additional stress factors operative in older infants, such as their emotional reactions to a strange environment, hunger, and separation anxiety. Alternatively, greater catecholamine responses may have resulted from direct or reflex stimulation of the efferent nerves supplying the adrenal glands during upper abdominal surgery.[32]

The significantly higher plasma concentrations of norepinephrine at baseline in the ventilated than in the non-ventilated neonates might be explained by the withdrawal of sedative and analgesic drugs before surgery (according to the study protocol) in a limited number of patients.

Preoperative neonatal plasma concentrations of lactate were comparable with those in previous studies.[10] Baseline values in the present study were not quite comparable with published results,[8 10] because the first blood sampling in the present study occurred after the administration of fentanyl anaesthesia, whereas in the other studies baseline samples were drawn before analgesia.

Neonates had lower pain scores and needed less morphine than older children, probably because of the increased morphine metabolism more than 4 weeks after birth, resulting from closure of the ductus venosus and maturation of hepatic enzymes.[33 34] We found no consistent correlation of physiological signals of acute pain (plasma concentrations of epinephrine and norepinephrine) with behavioural pain scores (VAS and COMFORT scale).

The results of the present study allow us to draw important clinical and physiological conclusions. We can resolve the clinical controversy regarding continuous *vs* intermittent morphine analgesia. We have shown that neonates and infants up to 1 yr of age can be given intermittent morphine doses, thereby avoiding excessive fluid intake and the need for infusion equipment. Older infants (1–3 yr) may require either a continuous infusion or more frequent dosing (every 1–2 h) or judicious increases in the intermittent doses used for postoperative morphine analgesia.

In addition, we have documented significant differences in hormonal and metabolic stress responses, physiological variables, behavioural responses and morphine consumption between neonates and older infants. These differences may result from the developmental changes in opioid pharmacology that occur in early infancy. Either neonates are unable to mount robust behavioural responses to postoperative pain or they may need less morphine for satisfactory behavioural pain scores. It is also evident that neonates need analgesia and/or sedation during mechanical ventilation in order to control catecholamine responses. In the different age groups between 4 weeks and 3 yr, we found similar patterns of hormonal-metabolic responses, behavioural responses and postoperative morphine consumption (although minor differences were found between infants aged 1–6 months and 1–3 yr).

We speculate that combined therapy with different classes of analgesic and sedative drugs will provide more effective control of physiological and behavioural responses, especially in children 1–3 yr of age, who may have a high level of anxiety in the PICU. Further studies are needed to establish the efficacy and safety of such combinations. We strongly support the recent editorial calling for more randomized clinical trials to investigate analgesic regimens in young children, due to the absence of validated clinical protocols for infants undergoing surgery.[15] Not only will these studies provide a scientific framework for the postoperative management of neonates and young infants, but they may also provide clues about the development of pain and stress-responsive systems in the developing brain.

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Cross-validation of a composite pain scale for preschool children within 24 hours of surgery

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This study was designed to cross-validate a composite measure of the pain scales CHEOPS (Children's Hospital of Eastern Ontario Pain Scale), OPS (Objective Pain Scale, simplified for parent use by replacing blood pressure measurement with observation of body language or posture), TPPPS (Toddler Preschool Postoperative Pain Scale) and FLACC (Face, Legs, Activity, Cry, Consolability) in 167 Thai children aged 1–5.5 yr. The pain scales were translated and tested for content, construct and concurrent validity, including inter-rater and intra-rater reliabilities. Discriminative validity in immediate and persistent pain for the age groups ≤3 and >3 yr were also studied. The children's behaviour was videotaped before and after surgery, before analgesia had been given in the post-anaesthesia care unit (PACU), and on the ward. Four observers then rated pain behaviour from rearranged videotapes. The decision to treat pain was based on routine practice and was made by a researcher unaware of the rating procedure. All tools had acceptable content validity and excellent inter-rater and intra-rater reliabilities (intraclass correlation >0.9 and >0.8 respectively). Construct validity was determined by the ability to differentiate the group with no pain before surgery and a high pain level after surgery, before analgesia ($P<0.001$). The positive correlations among all scales in the PACU and on the ward ($r=0.621$–0.827, $P<0.0001$) supported concurrent validity. Use of the κ statistic indicated that CHEOPS yielded the best agreement with the routine decision to treat pain. The younger and older age groups both yielded very good agreement in the PACU but only moderate agreement on the ward. On the basis of data from this study, we recommend CHEOPS as a valid, reliable and practical tool.

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Postoperative pain has been undertreated in children compared with adults.[1] One of the main reasons is the difficulty of assessing pain.[2] Preschool children usually lack the verbal and cognitive skills to describe their feeling of pain or physical discomfort. Pain assessment in this population depends on the observation and expertise of the care-provider. To date, many multidimensional composite measures that include self-report of pain in addition to behavioural and/or physiological indicators have been developed.[3] These pain scales, including CHEOPS (Children's Hospital of Eastern Ontario Pain Scale),[4] OPS (Objective Pain Scale, simplified for parent use by replacing blood pressure measurement with observation of body language or posture),[5 6] TPPPS (Toddler Preschool Postoperative Pain Scale)[7] and FLACC (Face, Legs, Activity, Cry, Consolability),[8] were validated in North American children immediately after emergence from general anaesthetics in the post-anaesthetic care unit (PACU).

The pain response is affected by several psychological factors, including cultural differences, observational learning, cognitive appraisal and coping style.[9] Cross-validation is needed in order to apply these measures in different cultures. Subsequent research has found that CHEOPS is ineffective in measuring pain which persists several hours after surgery. Beyer and colleagues found that the CHEOPS scores were generally very low and did not correlate well with a self-reported measure in children aged 3–7 yr.[10] Most scales in this group are highly correlated with CHEOPS and use many of the same behaviours, so it is likely that they

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would have similar problems. However, this speculation is based on extrapolation from one study, and more psychometric work is needed on these scales and their effectiveness in measuring persistent pain.[11]

The aims of this study were to cross-validate these composite measure pain scales in Thai children in terms of validity and reliability, to assess the discriminative ability of these measures during two periods (immediate pain in the PACU and persistent pain on the ward) and in two age groups (≤3 and >3 yr), and to assess the practicality of the tools.

Patients and methods

After obtaining approval from the ethics committee and informed written or oral consent from parents, we studied preschool children aged 1–5 yr who were undergoing general anaesthesia and surgery at Siriraj Hospital and the Queen Sirikit National Institute of Child Health, which are tertiary care hospitals in Bangkok, Thailand. Pain relief during anaesthesia was given according to the decision of the anaesthetists who had clinical care of the patients. The children were observed after awakening from anaesthesia until 24 h after surgery. Patients were excluded if they were ambulatory or had postoperative ventilatory support, chronic pain or developmental delay.

Baseline behaviours before and after surgery, before the administration of analgesia in the PACU and on the ward were recorded with a video camera which was hidden from view. A nurse called the researcher to record a videotape of the child's behaviour when she diagnosed pain. Criteria for the diagnosis of pain were discomfort, reflection of pain in eyes, moaning or a facial expression or grimace including complaint of pain with active or passive movement or without movement. Other causes of distress, such as hunger, thirst, nausea and vomiting, were relieved. Distraction techniques, such as telling stories, playing with toys and watching television, were attempted before pain was diagnosed. The decision to give analgesics was made by one of the researchers, who was unaware of the child's pain scale rating, which was based on observations in routine clinical practice combined with the patient's self-report (older children) and the parent's opinion (if available). Intravenous fentanyl 1 μg kg^{-1} or pethidine 0.5 mg kg^{-1} was given as analgesia in the PACU. On the ward, analgesics were prescribed by surgeons. Most children were given pethidine 1 mg kg^{-1} i.m. for moderate to severe pain and oral paracetamol 10 mg kg^{-1} for mild pain.

Patients who were not considered to have pain by both nurses and the researcher in the PACU were videotaped just before they left the PACU, and the behaviour was recorded as behaviour before analgesics were given. Similarly, if the patients on the ward were not considered to have pain during the period since the last analgesic, their behaviour was videotaped 6 h after the last analgesic was given and recorded as behaviour before the analgesic period.

The chronological sequence of the videotapes was rearranged into a new random sequence by a computer program in order to blind the observers. We trained four observers (nurse anaesthetists) to rate all the pain scales. The inter-rater reliability between the four observers was tested by rating 30 pain behaviours for each pain scale. All pain behaviours were randomized into four blocks. As the inter-rater reliability yielded a high score (intraclass correlation >0.9), each observer rated each block on a single occasion.

Cross-validations were performed by translation, validity testing and reliability testing.

Translation

The four pain scales were translated from English into Thai by an anaesthetist who was fluent in both languages. Then, another bilingual anaesthetist, who was not associated with the translation phase, translated the Thai version back into English. Finally, the back-translated scales were rechecked with the original scales by another translator whose mother tongue was English. Alterations were made on the basis of the third expert's opinion in order to produce the same meaning as the original scales.

Reliability testing

Reliability is a measure of consistency and was assessed as the intra- and inter-rater reliabilities. For intra-rater reliability, the observers were asked to rate 30 pain behaviours for each pain scale on a second occasion, 2 weeks after the first occasion. For inter-rater reliability, the four observers were asked to rate the same 30 pain behaviours for each pain scale.

Validity testing

Validity is a measure of accuracy, and was evaluated as follows.

Content validity

All pain scales were tested, on the basis of content relevance, coverage and scaling, by a paediatrician, a paediatric anaesthetist, a paediatric surgeon, a paediatric psychologist, a nurse and a kindergarten teacher. Content validity of each item was scored as 1=relatively valid, 0=not sure, −1=relatively irrelevant.

Construct validity

This is an assessment of the meaning of the instrument in terms of its theoretical basis by comparison with external variables related to the construct. We compared the scores for all four pain scales at no pain before surgery with those after surgery, before analgesia, as the postoperative pain scores were expected to be higher than those during the preoperative period.

Concurrent validity

Correlations of OPS, TPPPS, FLACC with CHEOPS were tested at the same point in time. We identified appropriate cut-off points for each pain scale, which yielded the highest agreement (κ value) with the clinical decision to treat pain.

Effectiveness of the measures

Discriminative capability

The agreement or κ value of the four pain scales and the routine decision to treat pain, including sensitivity and specificity, were assessed on the basis of time (immediately in the PACU and several hours later on the ward) and age group (⩽3 and >3 yr). Factors that might affect pain behaviour, such as previous surgery, the presence of the parents and the site of surgery, were also recorded.

Practicality of measures

After training in the use of the pain scales, 30 nurses rated 10 behaviours from a videotape on four pain scales. The time taken to rate each behaviour on each scale was recorded. The nurses were asked to rank the scales according to the feasibility of their use in clinical situations, ease of use, ability of the scales to help assess pain, and general satisfaction with the scales.

Statistics

The sample size was calculated on the basis of a descriptive study with a variation of 8% and incidence of absence of pain of 25%.[12] The formula $n=Z\alpha^2pq/\delta^2$ was used, $\alpha=0.05$, $p=0.25$, $q=1-p$, $\delta=0.08$. The estimated sample size was 113. Demographic data are presented as mean (SD), median (interquartile range) and 95% confidence interval. Content validity was assessed for each item by using item correlation (IC), which is the total score of each item divided by the number of experts. If IC is ⩾0.5, the item would be acceptable. Inter-rater and intra-rater reliabilities were analysed by intra-class correlation [$R=\sigma^2$ subject/(σ^2 subject+σ^2 observer + σ^2 error)]. An intra-class correlation of >0.8 was considered acceptable. As all pain scores were non-parametric data, discriminant validity was determined with the Wilcoxon rank sum test to assess the difference in pain scores before and after surgery, before analgesia. The correlations among CHEOPS, OPS, TPPPS and FLACC were analysed with the Spearman correlation. The agreement of all pain scales at various cutoff points, corresponding to the decision to treat pain in clinical practice, was analysed with the κ statistic. Values of κ were interpreted as follows: <0.2, poor agreement; 0.21–0.4, fair agreement; 0.41–0.6, moderate agreement; 0.61–0.8, good agreement; 0.81–1.0, very good agreement.[13] The appropriate cutoff point was that point which yielded the highest κ value, sensitivity and specificity. The differences in pain scores related to previous experience and parental presence were analysed with the Mann–Whitney *U*-test. The practicality of the scales, such as the time taken to rate the pain scores and the ranking of questionnaires, was analysed with descriptive statistics. All analyses were performed with SPSS for Windows v. 7.0 (SPSS, Chicago, IL, USA).

Results

Of the 167 patients enrolled in the study (age range 1–5.5 yr), who were recovering from most types of surgery (Table 1), 18 had missing PACU data and 28 had missing ward data. The pain severity resulting from these surgical procedures was classified as moderate to severe.[14]

The content validation of OPS and FLACC was accepted totally by all experts. Two behaviours in the CHEOPS score—upright behaviour (an alternative in item 'torso') and standing behaviour (an alternative in item 'leg')—produced disagreement as they were behaviours seen rarely in Thai children. 'Squint', an alternative in the item 'eye' of the TPPPS, was opposed for the same reason.

The inter-rater and intra-rater reliabilities of the four observers were excellent (Table 2). Construct or discriminant validity clearly demonstrated a significant difference in pain scores before and after surgery, before analgesia. The median pain scores on the wards were lower than in the PACU (Table 3).

Concurrent validity was assessed in terms of correlation. All data before analgesia, both in the PACU and on the ward, were analysed for association. The correlation of the four pain scales with each other was moderate to good (r=0.621–0.769, P<0.0001) in the PACU and good (r=0.757–0.827, P<0.0001) on the ward (Table 4).

Corresponding with the clinical decision to treat pain, the cutoff points which yielded the highest agreement for OPS, TPPPS and FLACC were 2, both in the PACU and on the ward. Based on the κ value, the cutoff point of CHEOPS on the ward (5) was lower than that of the PACU (6). However, in terms of pain scale content, patients with OPS, TPPPS and FLACC scores of >2 and a CHEOPS score of >6[15] [16]

Table 1 Patient characteristics and type of surgery (*n*=167)

Characteristic	**Value**
Age (yr), mean (range)	2 9 (1–5.5)
⩽3 yr, *n* (%)	97 (58)
>3 yr, *n* (%)	70 (42)
Experience of previous surgery, *n* (%)	56 (41)
Parent present, *n* (%)	102 (61)
Type of surgery, *n* (%)	
Maxillofacial and head-neck	40 (24)
Groin and perineum	35 (21)
Abdomen	34 (20)
Limb	22 (13)
Ear, nose and throat	17 (10)
Eye	11 (7)
Thoracic	5 (3)
Burn	3 (2)

Table 2 Inter- and intra-rater reliabilities for the pain scores CHEOPS, OPS, TPPPS and FLACC

Pain scale	**Inter-rater reliability**	**Intra-rater reliability Observer**			
		1	**2**	**3**	**4**
CHEOPS	0.9184	0.9819	0.9660	0.8733	0.9949
OPS	0.9198	0.9858	0.9503	0.9496	0.9945
TPPPS	0.9657	0.9957	0.9558	0.9232	0.9975
FLACC	0.9488	0.9707	0.9909	0.9506	0.9915

Table 3 Construct validity of pain scores before surgery and after surgery, before analgesia in the PACU and on the ward. Wilcoxon rank sum test

Pain scale	**Pain score: median (interquartile range)**			***P***
	Before surgery	**After surgery, before analgesia**		
		PACU	Ward	
CHEOPS	5 (4–5)	9 (7–10)	7 (5–10)	<0.001
OPS	0 (0–0)	5 (2–7)	2 (0–5)	<0.001
TPPPS	0 (0–0)	5 (3–6)	3 (0–5)	<0.001
FLACC	0 (0–0)	6 (2–8)	3 (0–5)	<0.001

Table 4 Correlations among CHEOPS, OPS, TPPPS and FLACC scores. Spearman correlation, $^*P<0.0001$

	PACU				**Ward**			
	CHEOPS	**OPS**	**TPPPS**	**FLACC**	**CHEOPS**	**OPS**	**TPPPS**	**FLACC**
CHEOPS	1.000				1.000			
OPS	0.752*	1.000			0.827*	1.000		
TPPPS	0.769*	0.694*	1.000		0.818*	0.761*	1.000	
FLACC	0.696*	0.721*	0.621*	1.000	0.817*	0.757*	0.791*	1.000

Table 5 Cutoff points which yielded the highest agreement (κ value) with the clinical decision to treat pain

Pain scale	**PACU (*n*=149)**				**Ward (*n*=139)**			
	Cutoff point	**κ**	**Sensitivity (%)**	**Specificity (%)**	**Cutoff point**	**κ**	**Sensitivity (%)**	**Specificity (%)**
CHEOPS	6	0.829	97	86	6	0.560	77	90
					5	0.620	85	84
OPS	2	0.607	83	87	2	0.341	61	88
TPPPS	2	0.745	90	92	2	0.461	91	70
FLACC	2	0.659	88	86	2	0.389	64	91

were considered to have pain. The agreement of CHEOPS with the clinical decision to treat pain was the highest among all scales both in the PACU and on the ward (Table 5).

According to age group, a cutoff point of 6 for CHEOPS in the PACU yielded very good agreement with the routine decision to treat pain in both age groups (≤3 and >3 yr) but there was only moderate agreement on the ward (Table 6).

The cutoff point associated with the highest κ agreement of all scales in the PACU provided high sensitivity and specificity (>80%). On the ward, a CHEOPS cutoff point of 5 yielded high sensitivity and specificity (>80%), but the discriminative abilities of a CHEOPS cutoff point of 6, OPS, TPPPS and FLACC were lower than this (Table 5). The result was similar in the younger and older groups (Table 6). Neither pain experience from previous surgery nor parental presence seemed to affect the severity of immediate or delayed postoperative pain (Table 7). Regarding the type of surgery, a high level of pain from eye surgery in the PACU was not seen on the ward (Table 8).

Table 6 Agreement of CHEOPS with the clinical decision to treat pain categorized by age group

	PACU		Ward			
	Age ≤3	Age >3	Age ≤3		Age >3	
Cutoff point	6	6	5	6	5	6
κ	0.838	0 818	0.640	0 560	0.588	0 515
Sensitivity	99	94	79	76	84	76
Specificity	81	92	85	80	83	92
n	84	65	82	82	57	57

Table 7 Postoperative pain scores related to previous surgery and parental presence. Mann–Whitney *U*-test

	CHEOPS: median, (interquartile range)/*n*			
	PACU	*P*	Ward	*P*
Previous surgery				
Yes	8 (7–10)/49	0.830	7 (5–10)/45	0.666
No	9 (7–10)/76		7 (5–9)/74	
Parental presence				
Yes	9 (7–10)/93	0 182	7 (5–10)/92	0 203
No	9 (8–10 5)/56		8 (6–10)/49	

Table 8 Postoperative pain scores related to site of surgery

Site of surgery	CHEOPS: median (interquartile range)/*n*	
	PACU	Ward
Maxillofacial, head–neck	10 (7.5–11)/35	7 (5–9)/33
Eye	10 (9–10.5)/11	5.5 (5–7)/6
Ear, nose, throat	9 (7 5–9)/16	7 (5.5–8)/15
Limb	8 (8–10)/21	7 (5–10)/21
Thoracic	7 5 (6–8.5)/4	8 (5–8)/5
Abdomen	8 (7–9 5)/28	7 (6–10)/32
Groin, perineum	8 (5–11)/31	8 (5 5–9 5)/27
Burn	9 (8–9)/3	8 (5–11)/2

Table 9 Practicality of pain scales

	CHEOPS	OPS	TPPPS	FLACC
Duration of rating (s)	59 0 (15 8)	44.1 (12 7)	40.1 (15 3)	45 5 (14 2)
Feasible for clinical use (% of respondents)	80	76 7	80	90
Easy of use (% of respondents)	83.3	73.3	73.3	73.3
Help in assessment (% of respondents)	100	83 3	80	86 7
Generally satisfied (% of respondents)	63 4	46.7	26 6	66.7

In terms of practicality, CHEOPS and FLACC were comparable except for the duration of rating with CHEOPS, which was longer (Table 9).

Discussion

Differences in culture and coping style may affect the behavioural responses of children. Some behaviours in CHEOPS and TPPPS were not accepted by our observers as they were rarely seen. However, these behaviours were alternatives to several choices in those items and even if they were excluded all items of CHEOPS and TPPPS could be scored properly. Therefore, the content validity of all four pain scales was considered to be appropriate on the basis of content relevance and coverage.

The construct validity of all pain scales was determined by comparing the group experiencing no pain in a baseline situation before surgery with the group experiencing a high level of pain after surgery, before analgesia. The difference in pain scores was clinically and statistically significant. The positive correlations of all scales with each other support concurrent validity. The stability and consistency of all the pain scales was proven by excellent inter-rater and intrarater reliability (intraclass correlation >0.8).

In terms of discriminative ability, assessment of pain in the PACU by all measures yielded higher agreement with the decision to treat than assessment of pain on the ward. The results were similar in the younger (1–3 yr) and older age groups (>3–5.5 yr). These findings support the study of Beyer and colleagues, who found that CHEOPS scores were generally low several hours after surgery and did not correlate well with self-report measures.[10] There are several possible reasons for the expression of fewer pain behaviours in persistent pain. First, the incidence of emergence delirium or agitation occurred most commonly in preschool-age children.[17] Pain combined with emergence agitation might increase the severity of behaviours observed in the immediate postoperative period.[18] Secondly, other causes of distressed behaviour cannot be distinguished from pain.[19] Children might gradually adapt themselves to this distress and reduce the severity of their pain behaviours as time passes. Thirdly, in the delayed postoperative period when the children are wide awake, older children, in particular, may behave in a socially desirable way or may underexpress their pain in order to avoid unpleasant medication (e.g. injection). Some of them may escalate their pain behaviour to obtain increased adult attention, especially when their parents are present. This study did not find any influence of experience of previous surgery and parental presence. Postoperative pain from eye surgery seemed to disappear more quickly than pain after other types of surgery.

Pain assessment and treatment decisions may be influenced by practice settings[20] and characteristics of the providers such as age, education and personal pain experience.[21] Research has shown that the use of a standardized pain assessment tool results in provider ratings of pain that more closely match the child ratings.[22] In order to implement pain scales in clinical practice, cutoff points were not reported for all tools in the original studies. Our discrimination points might be of benefit in treatment decisions in research and clinical settings. The cutoff points for OPS, TPPPS and FLACC corresponding with the decision to treat were all 2, both in the PACU and on the ward. On the basis of the contents, score 3 could represent pain behaviour.

Cutoff point 6 with CHEOPS in the PACU was similar to that found in other studies.[15] [16] A score of 7 was able to represent pain behaviour. Despite the fact that a CHEOPS cutoff point of 5 yielded the highest agreement with decision to treat, the contents of the CHEOPS score 6 derived from score 1 of 6 items (no cry, composed face, not talking, neutral body position, not touching wound and neutral leg position) might not necessarily represent pain behaviour. Therefore, in this study we decided to use a CHEOPS cutoff point of 6 on the ward. The agreement of CHEOPS with decision to treat was still higher than that of the other scales.

The behavior of all pain scales in Thai children appeared to be similar to that in North American children, and the different scores were all highly correlated. Among the four scales, CHEOPS yielded the highest agreement with decision to treat. Concerning practicality, FLACC and CHEOPS seemed to be similar, except that CHEOPS took about 14 s longer to rate. The time taken to rate may be decreased by further training. On the basis of our findings, we recommended using CHEOPS to assess pain in children aged 1–5 yr, especially in the immediate postoperative period.

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Volume kinetics of Ringer's solution during induction of spinal and general anaesthesia

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The kinetics of an i.v. infusion of 20 ml kg^{-1} of Ringer's solution over 60 min was studied in patients undergoing spinal (n=10) and general (n=10) anaesthesia. The induction resulted in similar changes in volume kinetic parameters in both groups. When a one-volume model was employed (n=8), however, the infusion expanded a smaller body fluid space in the four patients who had received preoperative enteric lavage (3.3 *vs* 8.3 litres), which is consistent with hypovolaemia. When a two-volume model was statistically justified (n=12), the induction reduced the rate of fluid equilibration between a fairly small central (V_1, mean 1.4 litres) and a peripheral body fluid space by about 50% (P<0.01). The kinetic analysis suggested that a rapid fluid load of 350 ml given over 2 min just after the induction could possibly prevent arterial hypotension because of central hypovolaemia. This was confirmed in five additional patients.

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The onset of spinal and epidural anaesthesia is often accompanied by acute arterial hypotension. Ringer's solution is usually infused for prophylaxis, although the effectiveness of such a measure has been questioned.[1–4] The poor preventive effect of fluid is difficult to understand as relative hypovolaemia is believed to be the cause of the hypotension. General anaesthesia also results in arterial hypotension, but its induction is associated with a generalized peripheral vasodilatation rather than a sympathetic block, which might imply that the body handles infused fluid differently than during spinal anaesthesia.

In the present study, we use volume kinetic analysis to compare the distribution and elimination of Ringer's acetate solution during the induction of spinal and general anaesthesia. The purpose of comparing these two situations is to obtain evidence as to whether the approaches for treatment should be the same. Furthermore, we wanted the kinetic analysis to possibly indicate how fluid can be used to prevent the hypotension.

Volume kinetics is based on the assumption that fluid given by i.v. infusion expands either one (V) or two (V_1 and V_2) fluid spaces in the body. The elimination of fluid from the system and the exchange of infused fluid between V_1 and V_2 are governed by the constants k_r and k_t, respectively.[5–11] Repeated measurements of the blood haemoglobin (B-Hb) concentration and urinary excretion were used on a computer-model to find estimates of the parameters in the volume kinetic models.

Patients and methods

Twenty patients between 33 and 93 (mean 67) yr of age with a body weight of 43–130 kg (mean 77 kg) undergoing elective surgery requiring general or spinal anaesthesia were studied. The choice of anaesthesia was made on clinical grounds by the anaesthetist (not by the research team). The operations in the spinal anaesthesia group involved inguinal hernia repair (n=2), femoro-popliteal vascular bypass surgery (n=6), and venous varices (n=2). In the general anaesthesia group, the procedures were cholecystectomy (n=4), repair of an abdominal aortic aneurysm (n=1) and resection of the colon (n=5). The male/female ratio in the first group was 5/5 and in the second it was 4/6. Medical conditions requiring chronic medication are presented in Table 1.

The protocol was approved by the Local Ethics Committee and the informed consent of all patients was obtained.

Enteric lavage, consisting of 4 litres of macrogol (Laxabon, Tika, Lund, Sweden) was given on the day before surgery to six patients scheduled for colorectal surgery. After fasting overnight, all patients underwent

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Table 1 Height and body weight, given as mean and SEM, and preoperative medical diseases requiring daily medication in patients scheduled for surgical procedures under spinal or general anaesthesia. Daily medication consisted in [a]salicylic acid, one patient in each group on β-blockers, [b]furosemide 40 mg

	Spinal anaesthesia (*n*=10)	**General anaesthesia** (*n*=10)
Height (cm)	169 (4)	171 (3)
Weight (kg)	75 (8)	78 (6)
Medical diseases		
Atherosclerosis[a]	5	3
Mild cardiac failure[b]	0	1
Diabetes, insulin	1	0
Diabetes, diet	1	0
Hypothyroidism	0	1
No disease	3	5

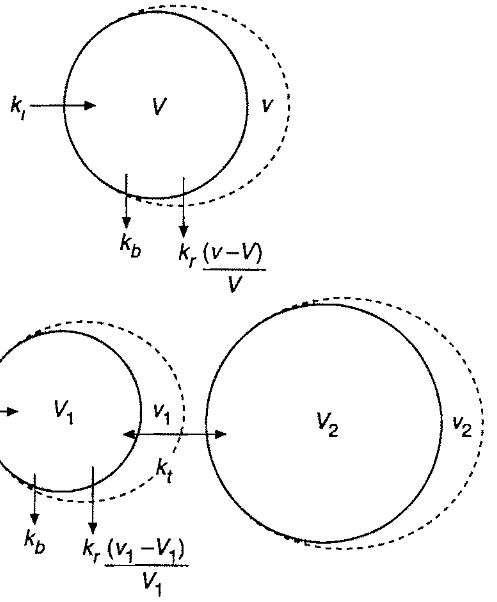

Fig 1 Schematic drawing of the one-volume kinetic model (top) and the two-volume kinetic model (bottom) used to calculate the size of the body fluid space expanded by i.v. infusion of fluid in humans

surgery, which started between 08:00 and 12:00. They received 5–7.5 mg of morphine by i.m. injection as premedication approximately 1 h before entering the operating theatre. With the patient in the supine position, a cannula was placed in the cubital vein of each arm for the respective purposes of sampling blood and infusing fluid. Fifteen minutes later, an i.v. fluid load of 20 ml kg^{-1} of Ringer acetate solution (Pharmacia, Uppsala, Sweden) was given at a constant rate over 60 min (0.33 ml kg^{-1} min^{-1}) via an infusion pump (Flo-Gard 6201, Baxter Healthcare, Deerfield, IL, USA). The Ringer solution had the following ionic content: Na 130, K 4, Ca 2, Mg 1, Cl 110 and acetate 30 mmol litre^{-1}.

Spinal (*n*=10) or general (*n*=10) anaesthesia was induced 20 min after starting the i.v. infusion. When spinal anaesthesia was induced, the patient was turned to a lateral position, and 2–3 ml of isobar bupivacaine 0.5% (Marcaine® spinal, AstraZeneca, Södertälje, Sweden) was injected. Immediately after injection, the patient was turned from the lateral back to the supine position. General anaesthesia was induced with thiopental 5 mg kg^{-1} and maintained with fentanyl 0.15 mg (mean dose) and 1–3% sevoflurane in oxygen and ambient air. Endotracheal intubation was facilitated by i.v. injection of rocuronium 0.5 mg kg^{-1}.

Monitoring included pulse oximetry and electrocardiography. Non-invasive arterial blood pressure was measured every 3 min in the arm not used for infusion by an automatic device (Datex AS3, Datex, Helsinki, Finland). Ephedrine 5–10 mg was given as an i.v. bolus if the systolic arterial pressure dropped below 60% of baseline. Surgery was not started until the study period was completed.

Venous blood (3.0 ml) was collected every 3 min during the study period of 60 min. A small discard sample was drawn before each blood collection to preclude any admixture of blood from the previous sampling. The cannula was rinsed with 2.0 ml of saline after each sample collection to prevent clotting. The B-Hb concentration was measured by a Technicon H2 device (Bayer, Tarrytown, NY, USA) with a coefficient of variation of 1%. The first sample was drawn in duplicate and the mean value was used in the calculations. The excreted urine was collected via an indwelling catheter, which had been inserted into the bladder under topical anaesthesia before the study started.

Additional patients

After the main study had been completed, five additional patients between 55 and 85 (mean 71) yr of age with a body weight of 50–103 kg (mean 77 kg) were studied to examine whether a specific fluid regimen suggested by the volume kinetic analysis of the first 20 patients is able to prevent arterial hypotension during the onset of spinal anaesthesia. The male/female ratio was 3/2 and the operations were similar as in the main study. In these additional patients, no preload was given but 350 ml of Ringer's solution was infused during as little as 2 min just after injecting the bupivacaine. Thereafter, the fluid was given at the 'normal' rate (0.33 ml kg^{-1} min^{-1}) during 40 min. The same measurements were performed as in the main study.

Calculations

The distribution of the fluid given by i.v. infusion was analysed using volume-of-fluid-spaces kinetic models, which can be summarised as follows (Fig. 1, top).

In the one-volume model, a fluid volume given by i.v. infusion at a rate k_i is distributed in an expandable space with a volume (v), which the fluid space strives to maintain at a target (baseline) volume (V). Fluid leaves the space at a controlled rate proportional with a constant (k_r) to the relative deviation of v from V, and also at a fixed basal rate (k_b). The increased dilution associated with spinal anaesthesia[12] and possibly also with general anaesthesia was assumed to represent a change in the size of V, for example, the model determined one size of V before anaesthesia was induced and another V for the time after the induction.

In the two-volume model, the primary fluid space (v_1) communicates with a remote fluid space (v_2). The rate of volume equilibration between the expandable fluid spaces is proportional to the relative difference in deviation from the target values (V_1 and V_2) by a constant (k_t) (Fig. 1, bottom). Here, the increased dilution associated with anaesthesia was assumed to represent a change in k_t, for example, the model determined one k_t before anaesthesia was induced and another for the time after the induction. The differential equations describing the volume changes in the expanded body fluid spaces as well as their matrix solutions are given in the Appendix.

The dilution of the plasma in the cubital vein was used to quantitate the water load as Ringer's solution remains outside the erythrocytes. As the sampled plasma is a part of V, we obtain the following dilution at time t:

$$(v(t)-V)/V=[\text{baseline B-Hb/B-Hb}(t) - 1]/(1 - \text{baseline haematocrit})$$

A correction for the loss of erythrocytes during blood sampling was made based on a preoperative blood volume estimated from the patient's height and body weight.[5]

The distribution of the infused i.v. fluid was modelled separately for each subject using Matlab version 5.2 (Math Works Inc., Notich, MA, USA), whereby a non-linear least-squares regression routine based on a modified Gauss-Newton method was repeated until no parameter changed by more than 0.001 (0.1%) in each iteration. The output of the kinetic analysis consisted in the best estimate and the standard error (SE) for V before and after induction (one-volume model) and for V_1 and V_2 as well as k_t before and after induction (two-volume model). However, the results of the latter analysis were reported only if an F test indicated that it was statistically justified.[6]

The following assumptions were made to ensure sufficient stability of the models: (1) k_r was calculated from the relationship between the integral of the dilution-time curve and the measured urinary excretion, both for the period of time up to when anaesthesia was induced and for the period thereafter.[6] (2) k_b was set to 0.8 ml min^{-1} (700 ml per 24 h) which is a reasonable estimation of the basal fluid loss (insensible water loss and baseline diuresis) from V. Half of this figure was assumed to appear as urine. (3) In the two-volume model, the individual curves were analysed after using a fixed value of V_2, assuming that the sum of V_1 and V_2 averages 12.5% of the patient's body weight, which is an average figure found in previous studies.[5–7]

Data are presented as the mean and (SEM) except where noted. Differences within and between the groups were studied using the one-way and repeated-measures ANOVA. Correlations between parameters were evaluated by linear regression analysis. $P< 0.05$ was considered significant.

Table 2 Volume kinetic parameters for loading with Ringer's solution during the onset of spinal (n=10) and general anaesthesia (n=10) The first line for each parameter in the one-volume and two-volume models gives the parameter estimate and the second line shows the SE associated with this estimate Data are given as the mean (SEM)

	Spinal anaesthesia	**General anaesthesia**
Urinary excretion (ml)		
Before induction	58 (16)	57 (21)
After induction	87 (27)	75 (31)
k_r *(ml min^{-1})*		
Before induction	40 (14)	62 (30)
After induction	10 (3)	10 (4)
One-volume space model		
N	4	4
V before induction (l)	8.27 (1.45)	3.28 (0.16)
SE	1.91 (0.51)	0.81 (0.35)
V after induction (l)	7.80 (1.06)	3.71 (0.51)
SE	1.17 (0.28)	0.53 (0.14)
Sum of squares (10^{-3})	7.9 (1.4)	7.2 (0.4)
Two-volume space model		
N	6	6
V_1 (l)	1.29 (0.32)	1.56 (0.21)
SE	0.42 (0.13)	0.45 (0.09)
k_t *(ml min^{-1})*		
Before induction	207 (48)	186 (31)
SE	80 (23)	65 (9)
After induction	112 (24)	94 (19)
SE	25 (11)	16 (3)
Sum of squares (10^{-3})	4.8 (0.6)	12.7 (5.5)

Results

The elimination rate constant (k_r) was reduced by the two forms of anaesthesia ($P<0.003$). After induction, k_r averaged only 10 ml min^{-1} (Table 2).

When the one-volume model was sufficient for an analysis of the data, the induction was not followed by a significant change in the size of V. However, V was smaller in the patients undergoing general anaesthesia ($P<0.02$), which means that the dilution of the plasma increased more in response to the infused fluid (Fig. 2).

The two-volume model was statistically justified in six of the patients in each group. The fairly rapid increase in haemodilution during the onset of anaesthesia (Fig. 2) is reflected in a decrease of k_t to ≈50% of baseline ($P<0.01$). In both groups, V_1 was only about 1.4 litres (Table 2).

The mean arterial pressure (MAP) tended to be higher before spinal anaesthesia (121 mm Hg) than before general anaesthesia (111 mm Hg) and the heart rate was lower (74 *vs* 83 beats min^{-1}), but these differences were not statistically significant (Fig. 3).

Induction of spinal anaesthesia reduced mean (SEM) MAP to 79 (4)% ($P<0.004$) and general anaesthesia to 70 (3)% of baseline ($P<0.001$; based on the average MAP recorded

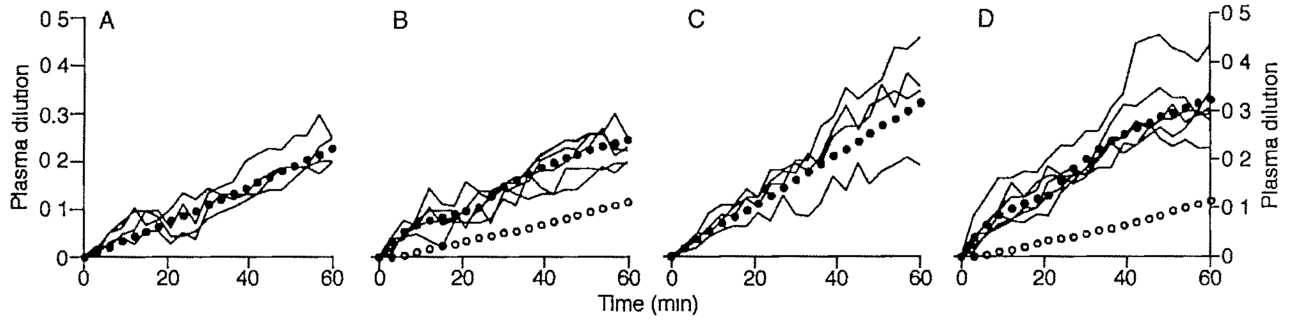

Fig 2 Dilution-time profiles in individual patients (thin lines) and the modelled dilution based on the mean parameter estimates shown in Table 2 (circles) during a continuous-rate infusion of Ringer's solution during which spinal anaesthesia (subplots A and B) or general anasthesia (subplots C and D) was induced after 20 min The one-volume space model was applied to the data in subplots A and C (closed circles=dilution of V) The two-volume space model was applied to the data in subplots B and D (closed circles=dilution of V_1, open circles=dilution of V_2)

between 0–18 and 27–60 min). This difference between the groups was statistically significant (P<0.05). Four patients in the general anaesthesia group and two in the spinal group received an i.v. injection of ephedrine to combat hypotension.

A search was made for factors correlating with the differences in kinetic parameters between individual patients. The decrease in MAP correlated with the size of V obtained after anaesthesia had been induced (one-volume model) and with the k_t obtained after anaesthesia had been induced (two-volume model; Fig. 4).

All six patients who underwent enteric lavage before surgery were in the general anaesthesia group. They tended to have a higher heart rate at baseline than the other patients (mean 89 *vs* 76 beats min^{-1}; P<0.06). Their drop in MAP was more pronounced (down to 63 *vs* 79% of baseline; P<0.001) and, in the four for whom the one-volume model was statistically justified, the size of V before anaesthesia was much smaller (3.3 *vs* 8.3 litre, P<0.02).

Simulations and additional patients

Simulations outlined the volume increment representing, in the two-volume model, the 'increased vascular costume' of V_1 associated with anaesthesia (Fig. 5, left). This increased haemodilution required 20 min to develop fully, and averaged only 125–150 ml. We hypothesized that such a volume increment would need to be filled up within a few minutes to prevent relative hypovolaemia in V_1 during the onset of the anaesthesia, but this seemed impossible with the mode of infusion used in the study (Fig. 6). The goal could be reached only with a short rapid infusion, and the infusion rates required to fill V_1 with various amounts of fluid within 2 min are shown in the right panel of Figure 5.

The additional five patients were studied to examine whether the infusion rate suggested to increase V_1 by 125–150 ml within 2 min according to Figure 5 is capable of preventing post-spinal hypotension. None of the additional patients required ephedrine, although their upper level of sensory analgesia was Th 5.6 (1.0) as compared with Th 6.4

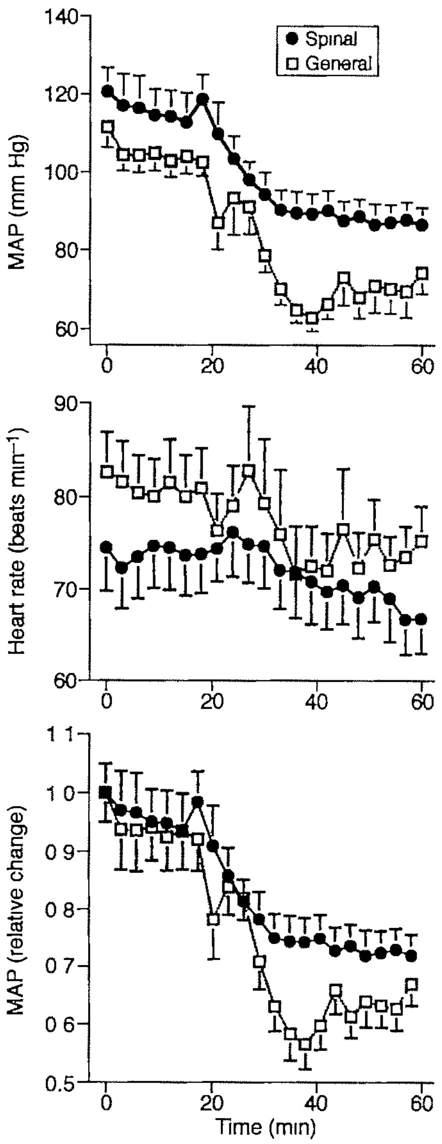

Fig 3 MAP (top) and heart rate (middle) when spinal or general anaesthesia was induced after 20 min of a continuous-rate infusion of 20 ml kg^{-1} of Ringer's acetate solution. The relative changes in MAP are also shown (bottom)

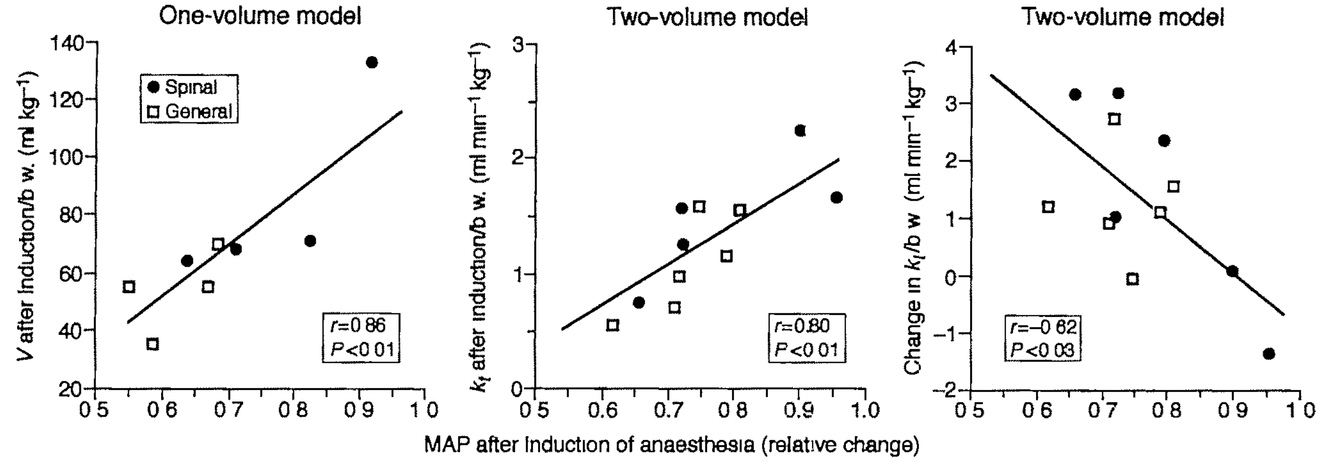

Fig 4 Relationships between the change in MAP during the induction of anaesthesia and the size of V after it had been induced in the eight patients in whom the one-volume model was statistically justified (left), to k_t after the induction (two-volume model, middle, one extreme outlier omitted) and to the difference in k_t from before to after the induction (two-volume model, right). The change in MAP was obtained as the mean of all measurements noted between 0 and 18 min divided by the mean obtained between 27 and 60 min of the study.

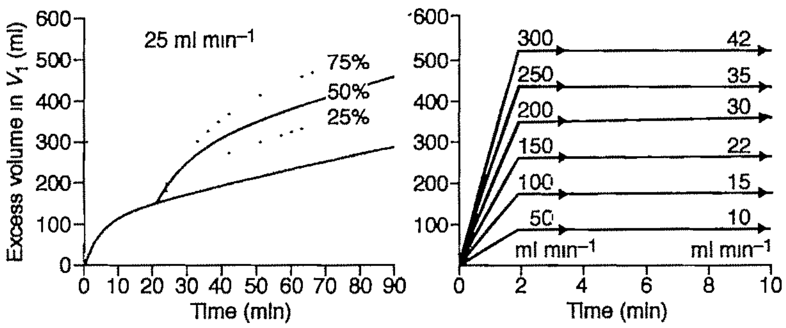

Fig 5 Computer simulations showing left: the excess volume in V_1 before and after the induction of anaesthesia in a subject with a body weight of 75 kg who received an i.v. infusion of 25 ml min^{-1} of Ringer's acetate solution. The increment between the solid lines represents, with a 50% probability, the increment in volume resulting from the anaesthesia. (Right) The infusion rates (ml min^{-1}) required to obtain, within only 2 min, a predetermined volume increase in V_1 during the onset of anaesthesia. The numbers to the right show the infusion rates required to maintain the volume increase obtained with the first more rapid infusion. Here, the initial phase of volume loading shown in the figure to the left has been omitted.

(0.7) in the other patients receiving spinal anaesthesia. MAP averaged 95 (5)% of baseline during 6 and 39 min after the induction, which a significantly smaller decrease than in the others (P<0.01; Fig. 7, top). Urinary excretion was 281 (64) ml (P<0.02 *vs* the others receiving spinal anaesthesia).

The one-volume model was sufficient to analyse the dilution-time curves in all the additional patients. The size of V for the 2-min rapid infusion was 4.44 (0.48) litres, while V for the subsequent slow infusion was 6.70 (0.60) litres (Fig. 7, bottom).

Discussion

Fluid resuscitation is commonly practiced to combat arterial hypotension during the onset of anaesthesia. The present study illustrates how the body, from a kinetic point of view, handles fluid in such situations. The method used for the study, volume kinetic analysis, has many similarities to pharmacokinetics but is based on the dilution of the venous plasma instead of the concentration of a drug in the blood. Volume kinetics has served as a tool for describing and simulating the distribution and elimination of Ringer's solution when infused in volunteers,[5–8] trauma patients,[9] and endotoxinaemic rabbits.[10] The modification of this mathematical approach employed here is intended to capture the change in volume kinetics from before to after a specific physiological event and has previously been applied to spinal anaesthesia during Caesarean section.[11]

In most patients, the kinetics of the infused fluid was described according to a two-volume model, which means that anaesthesia alters the rate of volume equilibration, expressed by a parameter k_t, between a central (V_1) and a peripheral body fluid space (V_2). The overall results indicate that the body handles infused fluid in a similar way during the induction of general and spinal anaesthesia. Both forms of anaesthesia were associated with a reduction k_t that was also of similar magnitude. Such a decrease of k_t quantitates an altered relationship in compliance between V_1 and V_2 with regard to volume expansion, which favours fluid accumulation in V_1.

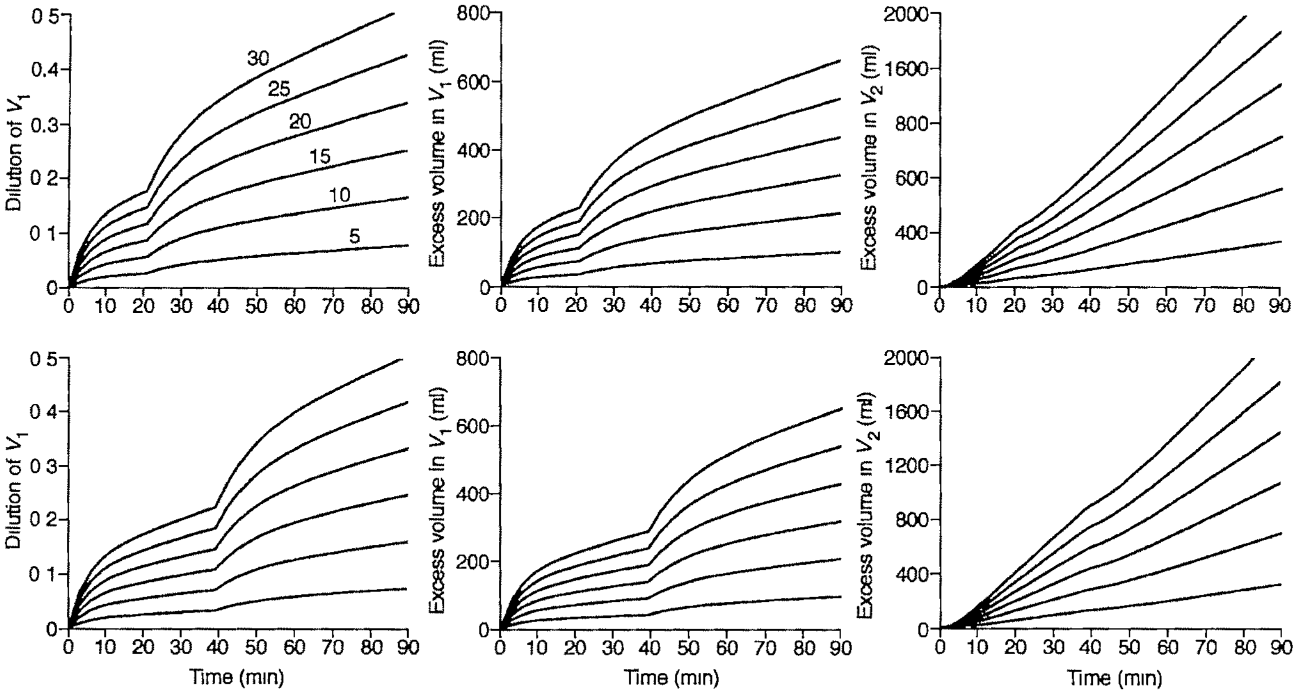

Fig 6 Computer simulations showing the predicted dilution of V_1 (left) and the excess volume in V_1 (middle) and in V_2 (right) when Ringer's acetate solution was infused at a rate of 5, 10, 15, 20, 25, and 30 ml kg^{-1} per 60 min in a subject with a body weight of 75 kg The upper row shows the situation when anaesthesia was induced after 20 min and the lower one when it was postponed until 40 min. All curves are based on the mean parameter estimates obtained for the 12 infusions for which the two-volume model was applied.

Another finding is that the size of V_1 was very small. In volunteer experiments, V_1 is usually close to the expected size of the plasma volume.[5–7] Most or all of the plasma volume was probably a part of V_1 during the initial 20 min of the present experiments too, but our partial derivative plots showed that the final estimate of V_1 was strongly affected by the increased haemodilution occurring just after the onset of anaesthesia. A problem in the curve-fitting procedure was that V_2 could not be estimated with confidence. Information about the size of V_2 is best obtained from post-infusion data, which were absent this time. The solution to the problem we used, which consisted in assuming a fixed sum of V_1 and V_2 as suggested by other studies, introduces some uncertainty about the pre- and post-infusion estimates of k_t, although their ratio is not changed.[11] In the present study, however, the estimates of k_t before the induction are similar to those obtained in volunteers.[5–7] Furthermore, the final estimate of V_1 is only marginally changed by setting different values for V_1+V_2.[11]

The combination of a small V_1 and a reduced k_t indicates that infused fluid circulates primarily in the central blood volume during the onset of anaesthesia. The resulting excessive dilution in V_1 represents an 'enlarged vascular costume', which correlates with the magnitude of the arterial hypotension that develops during the onset of epidural[12 13] and spinal[14] anaesthesia. The maximum dilution during epidural anaesthesia is developed 10–15 min after the drop in arterial pressure[13] and the present study shows that the time lag is the same during induction of spinal anaesthesia. Hypotension developed somewhat later after the induction of general anaesthesia, which is probably a result of the stress associated with the intubation procedure.

Spinal anaesthesia allows relative hypovolaemia to develop in the torso by shifting blood to the legs in healthy volunteers[15] and in patients with cardiac disease.[16] The preferential distribution of infused fluid to the central plasma volume, together with the slower transport of fluid to a more remote body fluid space, is a meaningful adaptation, as infused fluid then restores cardiac preload more effectively. Under these conditions, the vasodilated legs may become part of V_2. However, the infusion rates normally used for volume loading are simply too low to increase the volume of V_1 by 125–150 ml during the period of time between the injection of bupivacaine and the expected onset of hypotension 5–10 min later. Our data suggest that the strategy having the best chance to fill this increment, and which, therefore, might offer the best chance to prevent a drop in arterial pressure, would be to use a very high infusion rate just after the anaesthetic solution has been injected. Infusing fluid *before* the induction is less efficient as k_t is higher at that time. In the additional series of five patients, we challenged this hypothesis about preventing hypotension by giving 2-min rapid fluid load just after the

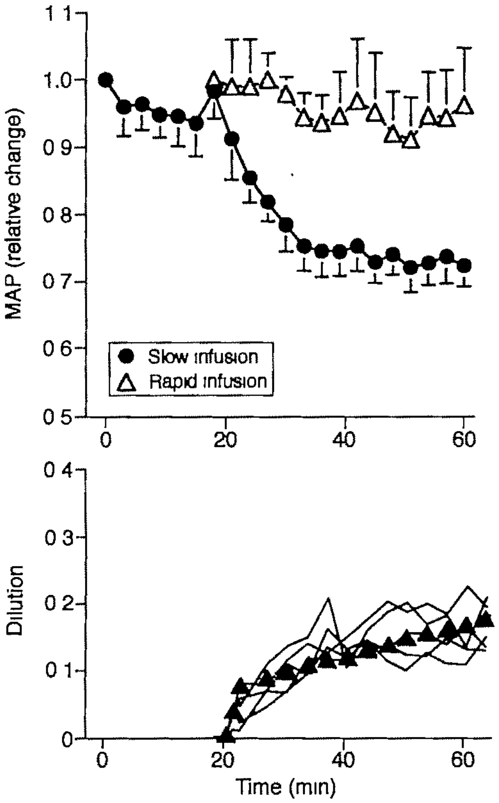

Fig 7 Spinal hypotension when i.v fluid is given at different rates. (Top) The relative change in MAP in patients receiving spinal anaesthesia at 20 min The first group ('slow infusion', n=10) were given 20 ml kg^{-1} of Ringer's acetate as a continuous infusion over 60 min, and the others ('rapid infusion', n=5) had their entire preload given between 20 and 22 min. (Bottom) The dilution-time profiles of the rapid infusion group and the modelled curve (dark triangles) based on the mean values of the volume kinetic parameters.

bupivacaine had been injected. Interestingly, no drop in MAP was observed, despite the fact that the analgesia was even more widespread in the additional patients than in the first 10 patients who received spinal anaesthesia. A follow-up study is planned to evaluate the clinical value of this fluid programme in a larger group of patients.

Another factor promoting central hypovolaemia when fluid is infused at a constant rate over 60 min fluid is that no recruitment of volume seems to occur from V_2 to V_1 during the onset of anaesthesia. Rapid transfer of fluid from muscle to the blood has been described when hypovolaemic stress is induced by a lower negative body pressure,[17] but virtually no haemodilution could be observed when epidural anaesthesia was induced without being accompanied by fluid.[12] Computer simulations based on the volume kinetic data derived here suggest that no such 'backward flow' would occur even if more prolonged volume loading was performed before induction of anaesthesia (Fig. 6, lower). However, the linear relationship between k_t after the induction and the relative change in MAP (Fig. 3, right) indicates that a transfer of fluid from V_2 to V_1 against a dilution gradient could occur when MAP falls to below 45% of baseline, as such a drop would theoretically result in a negative k_t.

Four patients in each anaesthesia group had their dilution-time curves analysed according to a one-volume model. The two-volume model was discarded in these cases as a statistical test indicated that estimating three parameters instead of two did not result in a significantly reduced mean square error of the differences between measured and model-predicted data on dilution.[5] Application of the two-volume model to these curves was possible but resulted in excessive SE for k_t both before and after the induction. The dilution over time increased in a linear fashion as more fluid was infused, and the plots lack the exponential shape of the two-volume dilution-time curves.

No effect of the induction of anaesthesia became apparent in the one-volume plots. One possible effect would consist in a reduction of V after the induction, resulting in a more pronounced dilution, as was found before Caesarean section.[11] A small V means that forces act to keep the infused fluid close to the bloodstream, similar to a low k_t in the two-volume model, and is associated with anaesthesia-induced hypotension (Fig. 4, left).

Enteric lavage given on the day before the operation seems to have affected the present results. This was not expected when the study was started, but its importance became apparent when we sought an explanation for the difference between spinal and general anaesthesia with respect to the pre-induction size of V in the one-volume model. V was small enough to even correspond to the expected size of the plasma volume, which is a sign of hypovolaemia, and we, therefore, believe that the patients were dehydrated by the lavage. This view is supported by the slightly higher baseline heart rate and the more pronounced drop in arterial pressure in these patients. The fact that lavage was employed only in the general anaesthesia group is sufficient to explain the smaller size of V among these patients as compared with those that received spinal anaesthesia.

Another possible confounder in the study was the occasional use of a small dose of ephedrine to alleviate severe hypotension (systolic pressure <60% of baseline). The doses given are likely to have slightly and transiently reduced the differences in blood pressure response between spinal and general anaesthesia. Ephedrine acts by increasing the cardiac output and, to some degree, by causing vasoconstriction. As argued previously,[11] this drug may have slightly reduced the vasodilatation and the rates of fluid exchange, but no indication of such effects could be obtained from the data. The effect of an i.v. dose of ephedrine is also fairly short. In contrast, the kinetic modelling was based on all data on haemodilution obtained during the 60 min of study.

An important finding is the weak diuretic response to volume loading. Only about 5% of the infused fluid volume of up to 2400 ml was excreted during the study period. The average half-life of Ringer's acetate, as extrapolated graphically, was between 150 min (one-volume model) and 500 min (two-volume model) before anaesthesia. The induction further inhibited the diuretic response and prolonged the half-life. In comparison, the half-life was approximately 15 min in elderly volunteers.[9] Preoperative stress and the overnight fast probably accounts for most of this difference. Interestingly, the diuretic response was stronger when the fluid therapy was started with a brisk 2-min infusion.

In summary, we found that induction of spinal and general anaesthesia results in similar changes in volume kinetic parameters and usually favoured an accumulation of infused fluid in a relatively small central body fluid space. The kinetic analysis suggests that the arterial pressure is better maintained by infusing fluid very rapidly just after the induction of anaesthesia than to give a preload.

Acknowledgement

The computer programs used were designed by Associate Professor Lennart Edsberg, Department of Numerical Analysis and Computing Science, Royal Institute of Technology, Stockholm, Sweden.

Appendix

The one-volume fluid space model is described by the following differential equation:

$$\frac{dv}{dt} = k_i - k_b - k_r \frac{(v - V)}{V} \tag{1}$$

which is solved as a monoexponential solution. Before induction of anaesthesia, it is

$$w(t) = \frac{(k_i - k_b)}{k_r} \cdot (1 - e^{-k_r/V}) \quad 0 \le t \le t_1 \tag{2}$$

and after (a) induction

$$w_a(t) = (w_1(t) - \frac{k_i - k_b}{k_r} \cdot e^{-k_r(t-t_1)/(V-\Delta V)} + \frac{k_i - k_b}{k_r} \qquad t_1 \le t \le \infty \tag{3}$$

where $w(t)$ is the dilution $(v(t) - V)/V$ and ΔV is the change in baseline (target) volume induced by the anaesthesia. k_r is calculated from the measured urine excretion and has different values during and after the induction of the anaesthesia.

The following differential equations describes two-volume fluid space model:

$$\frac{dv_1}{dt} = k_i - k_b - k_r \frac{(v_1 - V_1)}{V_1} - k_t \left[\frac{(v_1 - V_1)}{V_1} - \frac{(v_2 - V_2)}{V_2} \right] \tag{4}$$

$$\frac{dv_2}{dt} = k_t \left[\frac{(v_1 - V_1)}{V_1} - \frac{(v_2 - V_2)}{V_2} \right] \tag{5}$$

As with the one-volume model, the equations have been adapted for the special situation during anaesthesia, and they calculate one k_r for the period before and another k_r for the period after the induction. The form used to present the solution of equations 4 and 5 is based on the matrix exponential e^{At}, which is implemented as a standard function in the mathematical program Matlab. Before anaesthesia, we have

$$\begin{pmatrix} w_1(t) \\ \overline{w_2(t)} \end{pmatrix} = \frac{k_i - k_b}{k_r} \cdot (I - e^{At}) \cdot \begin{pmatrix} 1 \\ 1 \end{pmatrix} \qquad 0 \le t \le t_1 \tag{6}$$

and after (a) anaesthesia has been induced, it becomes

$$\begin{pmatrix} w_{1a}(t) \\ \overline{w_{2a}(t)} \end{pmatrix} = w_1(t) \cdot e^{A\,(t-t_1)} + \frac{k_i - k_b}{k_r} \cdot (I - e^{At}) \cdot \begin{pmatrix} 1 \\ 1 \end{pmatrix} \qquad t_1 \le t \le \infty \tag{7}$$

where the matrix A is

$$A = \begin{pmatrix} -(k_r + k_t)/V_1 & k_t/V_1 \\ k_t/V_2 & -k_t/V_2 \end{pmatrix} \tag{8}$$

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Patient-controlled analgesia for labour using remifentanil: a feasibility study

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We have investigated the efficacy and safety of remifentanil in a patient-controlled analgesia device for labour in 21 women. Remifentanil was available in increasing doses (bolus doses 0.25–1.0 μg kg^{-1}) with and without a background infusion (0.025–0.05 μg kg^{-1} min^{-1}). A lock-out time of 2 min was used. Thirteen out of 21 (62%) women chose to continue using remifentanil up to and during delivery. Nineteen out of 21 (90%) achieved a reduction in pain score from baseline. Using a VAS of 0–10 cm the median maximum reduction in pain score was 3 cm (range 0–8 cm). There was a significant reduction ($P<0.05$) from baseline pain scores (median=8 cm) to scores at bolus doses in the range 0.25–0.5 μg kg^{-1} (median=5 cm). There were no significant reductions in the fetal heart rate. Apgar scores and cord blood gas analyses remained within normal limits. We conclude that a remifentanil patient-controlled analgesia system (bolus doses 0.25–0.5 μg kg^{-1}, without a background infusion) may safely provide worthwhile, although incomplete, analgesia for labour.

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There is a need for an effective alternative to epidural analgesia in labour. Over 50% of women either choose not to have, or are unable to have, an epidural yet the only options for analgesia remain entonox, Transcutaneous Electrical Nerve Stimulation (TENS), intramuscular opioids such as pethidine, or alternative techniques, for example relaxation therapy, water bath, and aromatherapy. Entonox and pethidine are not without problems[1] and are of limited efficacy.

The use of pethidine as an analgesic for labour has recently been criticized.[2] This work demonstrated that pethidine acts as a sedative and not primarily as an analgesic. The timing of maternal injection is also a limiting factor as prolonged fetal depression is a well-documented side effect.[3 4]

Many women find that nitrous oxide is an unsatisfactory analgesic for established labour[5] and some are unable to use it effectively because of induced nausea and vomiting. Nitrous oxide may pose a risk to personnel working in areas where it is used for long periods of time without adequate scavenging facilities[6 7] and nitrous oxide emissions may be implicated in the 'green-house' effect.[8 9] There are increasing calls for the use of nitrous oxide to be reduced, or even abolished, in anaesthetic practice. Before remifentanil was available, no other analgesic had as rapid onset and termination of effect as nitrous oxide. Remifentanil may, therefore, have a unique role to play in obstetric practice where these characteristics are useful.

Remifentanil is a novel, ultra short-acting esterase metabolized synthetic opioid. It is a selective mu opioid agonist and has an ester linkage rendering it susceptible to rapid metabolism by non-specific blood and tissue esterases. Adult pharmacokinetic studies have shown a rapid onset of peak effect (blood–brain equilibration time: 1.2–1.4 min), a short duration of action independent of the duration of infusion (context sensitive half time: 3 min) and rapid clearance (40 ml kg^{-1} min^{-1}).[10–12]

These characteristics may make remifentanil a suitable drug for use in a patient-controlled analgesia system (PCA), with or without a background infusion, for analgesia in labour where severe pain occurs at intervals and rapid recovery between contractions and after delivery is desirable. The purpose of this study was to assess the feasibility of PCA remifentanil as an effective and safe alternative to epidural analgesia in labour.

The safety of remifentanil in obstetric patients and neonates has already been established by Kan and colleagues.[13] They used an i.v. infusion of remifentanil during

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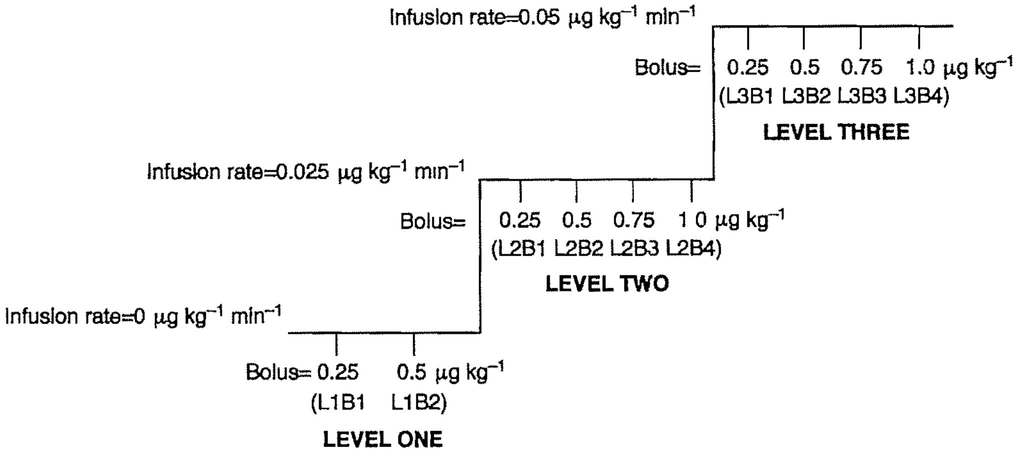
Infusion rate=0.05 μg kg⁻¹ min⁻¹
Bolus= 0.25 0.5 0.75 1.0 μg kg⁻¹
(L3B1 L3B2 L3B3 L3B4)
LEVEL THREE
Infusion rate=0.025 μg kg⁻¹ min⁻¹
Bolus= 0.25 0.5 0.75 1 0 μg kg⁻¹
(L2B1 L2B2 L2B3 L2B4)
LEVEL TWO
Infusion rate=0 μg kg⁻¹ min⁻¹
Bolus= 0.25 0.5 μg kg⁻¹
(L1B1 L1B2)
LEVEL ONE

Fig 1 Dose escalation for remifentanil PCA.

Caesarean section under epidural anaesthesia in a series of 19 patients. This study showed that placental transfer of remifentanil does occur but that it appears to be 'rapidly metabolized, redistributed, or both'. This study used a relatively high rate of infusion (0.1 μg kg^{-1} min^{-1}) but found there were no adverse effects on neonates. Mild maternal sedation and respiratory depression were noted but responded rapidly to a decrease in infusion rate. Remifentanil has also been used for post-operative analgesia in neonates and has been found to have a similar pharmacological profile in neonates to that of older children and adults.[14]

Remifentanil has been used extensively in awake non-obstetric patients as an infusion to supplement a regional technique or in the post-operative period.[15 16] Infusion rates of 0.05–0.1 μg kg^{-1} min^{-1} have been shown to provide satisfactory pain relief with any respiratory depression responding to small reductions in infusion rate.

There have been several case reports of remifentanil being used in a PCA device for labour in cases of thrombocytopaenia,[17 18] but this is the first formal evaluation of the feasibility of using a remifentanil PCA device, with or without a background infusion, for analgesia in normal labour.

Methods

After obtaining local Research Ethics Committee approval, 21 women (six nulliparous; 15 multiparous), ASA I or II, in established labour with the cervix at a minimum of 3 cm, were studied. Informed written consent was obtained. Patients that had already received pethidine or had requested an epidural were not studied. Other exclusions were twin pregnancy, pre-eclampsia, allergy to any agent under investigation, or failure to obtain informed consent. All patients were aware that remifentanil had not been used for this purpose before and were given a detailed information sheet.

All women had an i.v. cannula inserted (minimum 18-gauge) and i.v. fluids erected to run at 70 ml h^{-1}. A 20-gauge i.v. cannula was also inserted for the remifentanil PCA device. Non-invasive arterial pressure monitoring and pulse-oximetry were established and baseline arterial pressure, heart rate, Sa_{O_2}, respiratory rate, and fetal heart rate were recorded. Contractions were assessed using a Visual Analogue Scale (VAS) for pain. Each woman was asked to record the pain of her contractions on a VAS and also the smallest reduction in that pain which she considered to be worthwhile. The women then discontinued using entonox or TENS if appropriate. All women were aware that they could change to a regional technique at any time if they wished. All were shown how to use the PCA before starting the study and were instructed to press the button either as soon as they felt a contraction beginning or, in the case of those women having frequent regular contractions, whenever a contraction was anticipated. The bolus dose available from the PCA was increased in a stepwise manner and the effect of each dose was assessed after it had been used for 15 min.

There were three 'levels' in this study as shown in Figure 1. The patient progressed from level 1 to level 2 and finally to level 3. This progression was continued until either effective pain relief was reached or an adverse effect occurred. Each bolus dose at each level was available for 15 min. The PCA 'lock-out' time was initially set at 3 min. The first patient to be studied contracted at a rate of one contraction every 2 min and the 3 min lockout was, therefore, too long. The lockout time was subsequently reduced to 2 min. This 2 min lockout was, therefore, used in all remaining 20 patients. Levels 2 and 3 included a remifentanil infusion as shown. Arterial pressure, heart rate, Sa_{O_2}, respiratory rate, and fetal heart rate were recorded every 5 min.

After each 15 min period, the patient was asked to record the level of pain experienced during the preceding contractions on a VAS (the baseline VAS was not made available to the patient). Nausea, anxiety, sedation, and satisfaction

Table 1 Pain scores (VAS 0–10 cm) recorded during labour when using a remifentanil PCA Values are median (range)

Event	Median pain score (cm (range))
Baseline (using entonox, TENS)	8 (3–10)
L1B1 (bolus 0 25 µg kg^{-1}, no background infusion) after first 15 min	6 (2–10)
L1B1 (bolus 0.25 µg kg^{-1}, no background infusion) lowest score recorded	5 (1–10)
L1B2 (bolus 0.5 µg kg^{-1}, no background infusion) lowest score recorded	5 (0–10)
Delivery (using remifentanil, any dose)	8 (4–10)

scores were also recorded by the patient on a VAS. Any vomiting, dizziness, itching, or muscle stiffness was noted. Sedation was also recorded by the investigator using a score 1–5 (1=awake; 2=drowsy; 3=rousable to voice; 4=rousable to touch; 5=unrousable).

The stepwise increase in dose was stopped in the following circumstances: respiratory rate less than 8/min; Sa_{O_2} less than 90% for more than 15 s; mean arterial pressure decreased by more than 25% from baseline; heart rate less than 50 beat min^{-1}; fetal heart rate less than 110 beats min^{-1}; the patient was comfortable during contractions (VAS 3 or less); the patient was unwilling to continue.

The dose at which the patient reached the VAS that corresponded with 'the smallest reduction in pain that she considered to be worthwhile' was noted. The maximum safe dose, for example the dose before developing an adverse effect, was recorded if applicable. If analgesia was adequate at the end of the study period the patient was allowed to continue to use that dose for the remainder of labour. The investigating anaesthetist and the attending midwife were continuously present in the delivery room whilst the remifentanil PCA was being used.

At delivery, Apgar scores were noted at 1 and 5 min and cord blood was taken for blood gas analysis in every case. All women were asked for their comments about the PCA on the day after delivery. They were asked what they liked, what they disliked and for an overall comment.

Statistics

Parametric data were analysed by repeated measures ANOVA and simple summary statistics and non-parametric scores and scales were analysed by Friedman non-parametric repeated measures test.

Results

Out of 21 who started the study, 13 women (62%) continued to use the remifentanil PCA until delivery. The majority of these were multiparous patients (11 out of 13) and all 13 women had a normal delivery. Of the remaining eight women, four decided to change to a regional technique during the first stage of labour (one of these later required Caesarean section), one decided to change to a regional technique during a prolonged second stage (eventual forcep delivery) and three required a regional technique for delivery. One of these three requested spinal anaesthesia for a ventouse delivery and the remaining two women required a Caesarean section for failure to progress whilst using the remifentanil PCA. The mean (SD) age was 29 (7) yr and the mean (SD) weight was 78 (12) kg. The median (range) cervical dilatation reached before the PCA was started was 3 (3–6) cm.

A reduction in pain score from baseline was achieved in 19 out of 21 women (90%). Analgesia was, therefore, completely unsuccessful in two patients, one of whom was the first patient recruited to the study. The median maximum reduction in pain score achieved was 3 cm (range 0–8 cm) and in 17 out of 21 women (81%) this maximum reduction occurred at the level 1 dose range. Seven women (33.3%) achieved a reduction in pain score to VAS ≤3 cm and this occurred in all cases at the level 1 dose range. Ten women (48%) achieved the reduction in pain score that they had stated would be worthwhile and again this occurred in every case at the level 1 dose range.

The median pain score at baseline was 8 cm (range 3–10). When the baseline scores were compared with the lowest pain scores recorded at L1B1, bolus 0.25 µg kg^{-1} (median 5 cm), and at L1B2, bolus 0.5 µg kg^{-1} (median 5 cm), a significant reduction in pain scores was found ($P<0.05$). However, increasing the dose to the level 2 dose range (Fig. 1) did not result in any further significant reduction in pain scores. Thirteen women delivered using remifentanil and the median pain score at delivery was 8 cm (range 4–10 cm) (Table 1).

Maximum sedation (VAS) scores were significantly higher at L1B2, bolus 0.5 µg kg^{-1}, than at baseline ($P<0.01$). The observer sedation scores (1–5) were also significantly higher at L1B2, bolus 0.5 µg kg^{-1} (median score 2), than those at baseline (median score 1) ($P<0.05$). However, anxiety VAS scores were significantly reduced at L1B2 compared with baseline ($P<0.05$) and satisfaction VAS scores were significantly higher at L1B2 than at baseline ($P<0.01$) (Table 2). There was no significant increase in nausea VAS scores at L1B1 or L1B2 compared with baseline. Heart rate, systolic arterial pressure, and fetal heart rate did not change significantly at doses L1B1 or L1B2 compared with baseline.

Respiratory rate was significantly lower at L1B1, bolus 0.25 µg kg^{-1}, and L1B2, bolus 0.5 µg kg^{-1} than at baseline ($P<0.001$). The lowest respiratory rate recorded at the level 1 dose range was 10 breaths min^{-1} and the lowest rate

Table 2 Sedation, satisfaction, and anxiety scores (VAS 0–10 cm) recorded during labour when using a remifentanil PCA at level 1 dose range. Values are median (range). *P* value refers to comparison of baseline values with L1B2 values

Measurement n=20	Baseline (cm)	L1B1 bolus 0.25 μg kg^{-1} (cm)	L1B2 bolus 0.5 μg kg^{-1} (cm)	*P* value
Sedation VAS maximum score	2 (0–8)	4 (0–9.5)	6 (2–9.5)	<0.01
Satisfaction VAS maximum score	4.5 (0–8)	7 (2–9)	8 (2–10)	<0.01
Anxiety VAS minimum score	3 (0–9)	2 (0–5)	2 (0–4)	<0.05

Table 3 Patient comments about the remifentanil PCA on the day after delivery

Study number	Parity	Mode of patient of delivery (ND=normal delivery)	Patient comments on day after delivery
1	1	ND	(Patient changed to epidural as lockout too long)
2	2	ND	Remifentanil was better than entonox
3	1	ND	No comments recorded
4	1	ND	No comments recorded
5	0	Ventouse	Good for most of labour but not for later when pushing
6	0	ND	Would use again. Did feel drowsy but would not consider that a fault
7	4	ND	Did not like the way it made me feel. Epidural was much better
8	0	Caesarean	Great to control yourself. Instant effect when dose was increased
9	1	ND	Better than pethidine that I used with my first baby
10	2	ND	Better than pethidine. I felt more in control
11	1	Caesarean	Good for early labour but then I needed more pain relief and did not want to increase the remifentanil as it made me feel 'funny'
12	2	Caesarean	Felt in control and more clear headed than with pethidine. Excellent pain relief (sometimes I did not press the PCA to prove to myself that the pain was still there)
13	0	ND	Would use again. I felt in control. I did feel drowsy but this helped relaxation between contractions
14	1	ND	Better than pethidine. I liked being in control. It was difficult to co-ordinate pressing the PCA during pushing
15	1	ND	Better than pethidine. I felt in control and clear headed after delivery
16	2	ND	Better than pethidine. I felt more in control during labour and more alert afterwards. It was not good for pain relief for second stage but I would use it again
17	1	ND	Good until 8–9 cm, then only slight relief with each press. I felt less sleepy than with pethidine
18	1	ND	No comments recorded
19	1	ND	Very good, I would recommend it
20	0	ND	Good for early labour. I opted for epidural as I was making slow progress
21	0	Forceps	Good until 9–10 cm. I had a long second stage and found it hard to cope with the pain and, therefore, opted for a spinal

recorded at any dose was 8 breaths min^{-1}. None of the parturients required naloxone.

Six women experienced an adverse event as predetermined in the procedure; four women had oxygen saturations of <90% for more than 15 s, one had a sedation score of >3 and one had both a sedation score of >3 and an oxygen saturation of <90% for more than 15 s. These adverse events were all transient, responded rapidly to a reduction in dose and occurred at doses greater than level 1 (L2B2-L3B3) (Fig. 1). Vomiting occurred in 10/21 (48%) women, itch in 12/21 (57%) and dizziness in 9/21 (43%) at some point during the study. No muscle stiffness was noted. The mean total dose of remifentanil used was 2241 μg (range 340–6120 μg). Median Apgar scores at 1 and 5 min were 8 (range 5–9) and 9 (range 8–10), respectively, and the mean cord pH was 7.34 (range 7.24–7.43). No baby required naloxone to establish spontaneous respiration. One baby was given naloxone in addition to oxygen but began effective breathing instantly after the injection and it was considered unlikely that the naloxone had been necessary in that case. A fetal heart rate below 110 beats min^{-1} occurred on two occasions only. In one case, there was a rapid labour and delivery and the fetal heart rate fell transiently to 96 beats min^{-1} just before delivery. In the second case there was also a rapid labour and delivery and the fetal heart rate repeatedly dipped to below 110 beats min^{-1} during contractions in the short second stage. In both these cases, the impression was that these findings were probably secondary to the nature of the delivery. The heart rate immediately after delivery in both these cases returned to normal.

The women's comments on the day after delivery about the PCA are summarized in Table 3.

Discussion

In our study, PCA of remifentanil, without a background infusion and at bolus doses of up to 0.5 μg kg^{-1} (level 1 dose range) was safe in women in established labour. This dose range was effective in reducing pain scores for contractions from baseline levels.

Remifentanil has a unique metabolism by non-specific esterases which results in reduced pharmacokinetic variability and an extremely rapid clearance and offset of effect that is independent of excretory organ function or duration of use. This flexibility and lack of cumulating suggests that remifentanil has advantages over other methods in situations requiring intermittent pain relief followed by rapid recovery, such as labour. Some problems remain, notably the 90 s delay to peak drug effect and the usual mu agonist side effects.

We set out to investigate whether remifentanil could provide safe and useful analgesia for labour when given in a PCA system. The use of bolus doses of remifentanil in awake patients is controversial with some questioning the technique in patients whose airway is unsecured. Although muscle rigidity has been highlighted as a potential problem, when bolus doses of remifentanil were compared with equipotent doses of alfentanil the incidence and severity of this complication were similar.[19] It is worth noting that doses of remifentanil less than 2 $\mu g\ kg^{-1}$ given over 1 min have not been reported to cause muscle rigidity. Bolus doses as high as 1 $\mu g\ kg^{-1}$ have been used in awake patients.[20] In our study, none of our patients showed evidence of muscle rigidity or serious respiratory depression and, in our judgement, remifentanil PCA (0.05 $\mu g\ kg^{-1}$ boluses) did not increase the risk of regurgitation and aspiration.

Since our study began there have been two case reports of remifentanil used in a PCA system for labour.[17 18] One reported a 2 min lockout time with bolus doses ranging from remifentanil 35–75 μg. Interestingly, the remifentanil was purposefully discontinued in each of the three women when the second stage began.[17] The second report used a much smaller bolus dose (20 μg) and a longer lockout time (3 min).[18] Both reports concluded that remifentanil provided good analgesia for labour.

It was necessary to instruct the parturients in the use of the PCA system. The majority of women readily understood this as similar instruction is given for the use of entonox. Occasionally, analgesia was such that the women were only aware of the peak of the contractions and pressed the button too late. In most of these cases, the assistance of the midwife was invaluable in informing the woman that a contraction was starting.

The assessment of pain relief in labour is not straightforward. The pain experienced is not constant so that what is recorded as the 'worst pain imaginable' (10 cm on a VAS) by a woman in early labour may in fact be less severe than that recorded at 8 cm on a VAS at a later stage. Early retrospective assessment of labour pain (2 h post-delivery) considered with the duration of labour may help solve these difficulties.[21] However, in order to assess the efficacy and safety of increasing doses of remifentanil, we recorded VAS scores for pain every 15 min during remifentanil use.

Nineteen women (90%) achieved a reduction in pain score. These were meaningful reductions as even a 1 cm change in VAS score is considered to be clinically significant by patients.[22] Pain scores, as expected, tended to increase as labour progressed. Perhaps the best measure of satisfaction with remifentanil as an analgesic was the number of women who chose to continue to use the remifentanil up until delivery. All women were aware that they could change to an epidural and were encouraged to do so if their pain scores rose significantly as labour progressed.

The bolus dose range that provides effective analgesia in labour was clearly demonstrated by our study. Bolus doses at 0.25–0.5 $\mu g\ kg^{-1}$ without a background infusion (the level 1 dose range) were responsible for the maximum reduction in pain score in 17/21 women. All women recording either a pain score of three or less, or those recording the reduction in pain score that they thought to be worthwhile, also did so at the level 1 dose range. Analysis of pain scores revealed that increasing the dose from level 1 and, therefore, including a background infusion did not result in lower pain scores.

These findings appear to contradict those of a recent study that concluded that systemically administered opioids had no significant analgesic effect in labour.[2] In this small study, pain scores during established labour were compared at baseline, and after three contractions, after an i.v. dose of morphine or pethidine. It is not stated whether the women were also using entonox or TENS during these measurements. The dose of opioid was repeated twice and pain scores recorded each time after three more contractions. In our study, pain scores at baseline had a median value of 8 cm. After using the remifentanil PCA for 15 min (at a bolus dose of 0.25 $\mu g\ kg^{-1}$), the median pain score was reduced at 6 cm. If these two sets of pain scores are considered separately from the other data, a significant reduction in pain scores can be demonstrated ($P<0.001$) using the Wilcoxon signed rank test. It is not possible to continue the comparison of the two studies further as in our study the subsequent doses of remifentanil were not constant. It would seem likely that remifentanil has a better analgesic effect than pethidine or morphine, although it is difficult to be certain of equivalence in dosage. Further studies are needed.

The maternal safety of the level 1 dose range was also well demonstrated in our study as all adverse events occurred at level 2 or 3. In our study, 5/21 (24%) women had at least one episode of significant desaturation whilst using the remifentanil PCA. This compares favourably with an incidence of desaturation of 42% in women using entonox during labour.[23] We recommend, however, that pulse oximetry monitoring is carried out on all women using a remifentanil PCA in labour until more information is available. Adding a background infusion does not reduce pain scores but serves only to increase respiratory depression and sedation.

The incidence of vomiting was high, occurring in 10/21 (48%) women. However, only three women required antiemetics and only 3/21 women vomited whilst using remifentanil at the level 1 dose range. The occurrence of vomiting in low-risk normal labour has been reported to be as low as 19%.[24] However, when pethidine is used for analgesia in labour, vomiting has been reported in 40% of women,[2] which approximates to our incidence of 48%. Itch was reported in 12/21 (57%) women but this was described as mild and required no specific treatment.

Fetal heart rates, Apgar scores, and cord pH values were satisfactory. It was particularly reassuring that, despite remifentanil being available to the women at delivery, all Apgar scores at 5 min were in the normal range of 8–10 and that no baby required naloxone to establish spontaneous respiration. A forthcoming study will investigate cardiotocograph changes and the neurological and adaptive capacity score associated with using the remifentanil PCA.

In conclusion, remifentanil PCA with a bolus dose in the range 0.25–0.5 $\mu g\ kg^{-1}$ and a lockout time of 2 min appears a safe and effective drug for use in labour in patient-controlled analgesia systems. The technique appears to be most beneficial in multiparous women, 73% of whom chose to use the remifentanil PCA alone for their entire labour and delivery.

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Quantitative EEG changes associated with loss and return of consciousness in healthy adult volunteers anaesthetized with propofol or sevoflurane

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Significant changes in topographic quantitative EEG (QEEG) features were documented during induction and emergence from anaesthesia induced by the systematic administration of sevoflurane and propofol in combination with remifentanil. The goal was to identify those changes that were sensitive to alterations in the state of consciousness but independent of anaesthetic protocol. Healthy paid volunteers were anaesthetized and reawakened using propofol/remifentanil and sevoflurane/remifentanil, administered in graded steps while the level of arousal was measured. Alterations in the level of arousal were accompanied by significant QEEG changes, many of which were consistent across anaesthetic protocols. Light sedation was accompanied by decreased posterior alpha and increased frontal/central beta power. Frontal power predominance increased with deeper sedation, involving alpha and, to a lesser extent, delta and theta power. With loss of consciousness, delta and theta power increased further in anterior regions and also spread to posterior regions. These changes reversed with return to consciousness.

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Several attempts have been made to describe anaesthesia-induced topographic changes in the EEG. These studies relied upon conventional EEG with visual interpretation[1 2] despite problems with EEG variability across patients and anaesthetics and the subjectivity of conventional EEG interpretation.[3 4] Anaesthesia induction was associated with a frontal increase in beta activity that spread to more posterior regions as sedation level was increased and consciousness was lost. Delta activity appeared in posterior regions and migrated towards frontal regions. These observations of anaesthesia-induced EEG changes were summarized by the term 'frontal predominance'.[5] Frontal/central increases in beta1 (12.75–20.0 Hz) activity have been proposed as the most reliable indicators of sedation with propofol, although beta2 (20.25–30.0 Hz) and alpha2 (10.25–12.5 Hz) activity also increased.[6] Isoflurane/N_2O inhalation was shown to result in frontal alpha dominance.[7] However, none of these reports enabled direct comparisons across different anaesthetics, all used subjective rather than objective evaluation of EEG changes, and all failed to take account of individual EEG variability before the initiation of anaesthesia.

Improvements in quantitative EEG (QEEG) techniques have included computer extraction of quantitative EEG measures evaluated statistically using standard scores relative to the EEG obtained from a database of normal awake adults (i.e. neurometrics).[8] The present study examined changes in QEEG standard scores associated with the loss and return of consciousness in healthy normal volunteers who were anaesthetized with a technique using i.v. propofol and one using inhalation of sevoflurane. The purpose was to identify those QEEG variables that reliably

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reflected sedation level and the loss and return of conscious awareness by showing similar changes during the two anaesthetic protocols.

Subjects and methods

Subject population

The subjects were eight male and eight female ASA I paid volunteers between the ages of 20 and 40 yr (mean 30.3, SD 6.3), tested with two different anaesthesia protocols (the order was randomized), with at least 30 days between sessions. This study was approved by the Committee on Studies Involving Human Beings and written informed consent was obtained from each volunteer. All 16 volunteers completed the propofol protocol and 14 completed the sevoflurane protocol (two volunteers withdrew for personal reasons unrelated to the study).

Anaesthetic protocols

Both anaesthetic protocols were designed to parallel those in current clinical use at Brigham and Women's Hospital and to minimize risk and discomfort within our volunteer population. Premedication was either fentanyl 50 μg plus midazolam 1 mg or fentanyl 50 μg plus saline (randomized). An additional 50 μg of fentanyl was given to one volunteer during propofol administration because of discomfort associated with the placement of an arterial sampling line for obtaining propofol serum concentrations. Blood pressure, ECG, peripheral arterial oxygen saturation and axillary temperature were monitored. Anaesthesia was induced using age-corrected 0.1 minimal alveolar concentration (MAC=end-tidal concentration at which 50% of the population will move to a painful stimulus) steps for sevoflurane [based on the package insert for Ultane (sevoflurane); Abbott Laboratories, Chicago, IL, USA], or equivalent increments for propofol [MEC_{50}=minimal effect-site concentration at which 50% of the population will move to a painful stimulus (6 μg ml^{-1})][9] in combination with an infusion of remifentanil set to achieve a target effect-site concentration of 0.5 ng/ml (a concentration known to minimize chest wall rigidity). Propofol and remifentanil were administered at targeted effect-site concentration steps using the StanPump (developed by S. Schafer, from whom it is available free of charge) computer-assisted infusion technique. (The pharmacokinetic profiles for propofol and remifentanil used were from Gebts E, Camu F, Cockshoff ID, *et al.* Disposition of propofol administration as constant rate intravenous infusions in humans. *Anesth Analg* 1987; 66: 1256–63 and Minto CF, Schnider TW, Egan TD, *et al.* The influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology* 1997; 86: 10–23 respectively.) Sevoflurane was administered with end-tidal concentrations monitored with a calibrated Ohmeda gas concentration monitor (Datex Ohmeda – Anesthetic gas monitor, Instrumentarium, Helsinki, Finland) in steps of 0.1 MAC using an overpressure technique (Hewlett-Packard 58 gas chromatograph with flame ionization detection, Agilent, Inc., USA; Harvard Medical School).

Anaesthesia was administered in incremental 0.1 MAC/MEC_{50} equivalent steps in both protocols until loss of consciousness (LOC), and then increased to 0.7, 1.0 and 1.4 MAC/MEC_{50}. Once at 1.4 MAC/MEC_{50}, the target concentration of remifentanil was increased to 6.75 ng ml^{-1}, succinylcholine 1.5 mg kg^{-1} and laryngeal lidocaine spray 100 mg were administered, and the trachea was intubated. The remifentanil target concentration was then reduced to 1.75 ng ml^{-1} and the anaesthetic concentration was reduced in steps of 0.1 MAC/MEC_{50} until the return of consciousness (ROC). After each targeted hypnotic drug concentration had been achieved, the new concentration was maintained for an additional 8–10 min while the EEG and a measurement of level of arousal were obtained. LOC and ROC were defined using the measure of level of sedation described below.

In the propofol protocol, propofol and remifentanil concentrations were obtained at LOC, 0.7 and 1.0 MEC_{50}, and ROC, from blood samples acquired from a radial artery catheter for comparison with targeted plasma concentrations. Propofol plasma concentrations were based upon duplicate 2 ml samples using gas chromatographic separation with a 15 m × 0.53 mm internal diameter (ID) column with 1.5 μm 10B-5 film thickness and flame ionization, and accuracy was assessed using plasma samples with known drug concentrations. Remifentanil concentration was determined in duplicate citric acid-preserved arterial samples, with remifentanil separated using a 4 m × 0.25 mm ID DB-5 column with 0.75 cm film thickness, and high-resolution mass spectrometry with selective ion monitoring. Remifentanil concentrations of 0.026–8 ng μl^{-1} served as controls (mass spectrometer Uh70-V5H; Fison Instruments Inc., Rochester, MN, USA).

Measurement of level of sedation

After each targeted effect-site concentration had been achieved, the volunteer's level of sedation was measured immediately after the EEG had been collected, using a modification of the responsiveness component of the Observers Assessment of Alertness and Sedation scale (OAAS).[10 11] The following scoring system was used: 5=responds readily to command spoken in normal tone; 4=lethargic response to command spoken in normal tone; 3=lethargic response to command spoken loudly and repeatedly; 2=displays an appropriate response to command only after a loud verbal command and a mildly painful stimulus (train of four); 1=displays an appropriate response to command only after a loud verbal command and a moderately painful stimulus (50 Hz electrical stimulation for 1 s); 0=no response to verbal command with painful stimulus. Both painful electrical stimuli were applied to the wrist using a constant current stimulator set at 40 mA. Loss of the eyelash response was always found before checking a volunteer's sedation level below an OAAS score of 3. Using this scale, a score of less than 3 but greater than 0 represents the ability to respond appropriately to a loudly spoken verbal command accompanied by a painful electrical stimulus. In this situation it was important to differentiate an appropriate response to command from a response representing a pain-induced aversive or flexion reflex. An appropriate response to command after a painful stimulus was considered to result from a return to consciousness after it was lost. Failure to show an aversive movement to a loudly spoken verbal command with concurrent painful stimulation represented an anaesthetic depth that was equal to or greater than MAC/MEC$_{50}$. In all analyses presented below, the LOC end-point used was a score of 0.

EEG acquisition

EEG was collected before premedication, after premedication and at each step of the protocol during and after equilibration at each drug concentration, as determined by the StanPump readout. All EEG data were collected with the eyes closed and the volunteer lying comfortably in a holding area or in an operating theatre suite. Gold cup electrodes filled with collodion were placed over 19 standard regions defined by the international 10/20 system, referenced to linked ears. All electrode impedance levels were kept below 5000 Ω. The EEG amplifiers had an acquisition bandpass from 0.5 to 100 Hz (3 dB points) with a 60 Hz notch filter. Differential recording channels were used to monitor eye movement artefact, movement artefact and the ECG. One minute of artefact-free EEG (twenty-four 2.5 s epochs) was selected by visual editing of the continuous EEG that was recorded after equilibration had been reached for each stage of the protocol. The artefact-free EEG was converted from the time to the frequency domain using a fast Fourier transform (FFT).[12] This paper will concentrate on one QEEG feature set: absolute power, the amount of energy (μV^2) within the delta (1.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 HZ), beta (12.5–25.0 Hz) and total (1.5–25.0 Hz) frequency bands.

Statistical methods

Anaesthetic delivery accuracy was evaluated using Pearson product moment correlations between the target and actual drug concentrations at each stage of the protocol. QEEG data analyses were accomplished as follows. Each QEEG feature was expressed as a Z-score (standard score) relative to the mean and standard deviation of the same QEEG feature obtained from an age-regressed, normalized data base of 250 normal awake adults.[13 14] The Z-scores for absolute power features collected in the non-medicated, baseline state were compared with those obtained after premedication, and during induction and emergence separately for sevoflurane and propofol anaesthesia. QEEG absolute power differences between sevoflurane and propofol during induction and emergence from anaesthesia were also examined, as were differences as a function of remifentanil concentration. The same statistical procedures were applied for all comparisons. One-way repeated measures analyses of variance (ANOVAs) were calculated for each of the 19 monopolar leads within each frequency band. The F' values and the averaged Z-scores associated with these comparisons are displayed in Figs 2–4. The colour-coding in Fig. 2 is proportional to the mean Z-score of each averaged sample. The significance of the mean Z-scores in these maps can be determined by taking into account the square root of the sample size. Thus, the 0.0001 level of significance for the propofol group with n=16 is 1.11 (4.42/4), and for the sevoflurane group with n=14 it is 1.14 (4.42/3.74). Because multiple analyses of variance were calculated, rigorous criteria for significance were used to interpret each ANOVA. Only P values less than or equal to the 0.001 level were considered significant.

Results

Predicted vs actual anaesthetic concentrations

The Pearson correlation between predicted and measured propofol plasma concentration was 0.89, between predicted and measured remifentanil plasma concentration 0.79, and between targeted and measured end-tidal expired sevoflurane concentration 0.97, with P<0.001 for all three correlations. Figures 1A and B show these relationships for propofol and sevoflurane. The mean plasma concentrations of propofol were 3.44 (SD 1.5) and 2.55 (0.8) μg ml^{-1} at LOC and ROC respectively. The mean StanPump predicted propofol effect-site concentrations were 2.52 (1.1) and 1.96 (0.5) μg ml^{-1} at LOC and ROC. End-tidal expired sevoflurane concentrations were 0.43 (0.17) and 0.26 (0.07) MAC at LOC and ROC. The mean measured plasma concentration of remifentanil was 0.48 (0.16) ng ml^{-1} at LOC and 1.4 (0.4) ng ml^{-1} at ROC.

Arousal level during LOC and ROC

In the majority of volunteers, changes in sedation level during induction were discontinuous, not passing through all steps in the OAAS scale. In most volunteers, failure to respond to a loud verbal command was the induction end-point, and subsequent painful stimulation was unable to re-establish consciousness. However, 3/14 sevoflurane and 7/16 propofol subjects (total=33.3%) were not aroused to loud verbal commands or train-of-four stimulation but regained consciousness after 50 Hz painful stimuli. During emergence in both protocols, ROC was elicited initially by a verbal command alone, 4/15 sevoflurane and 2/16 propofol volunteers showing an appropriate response initially to a

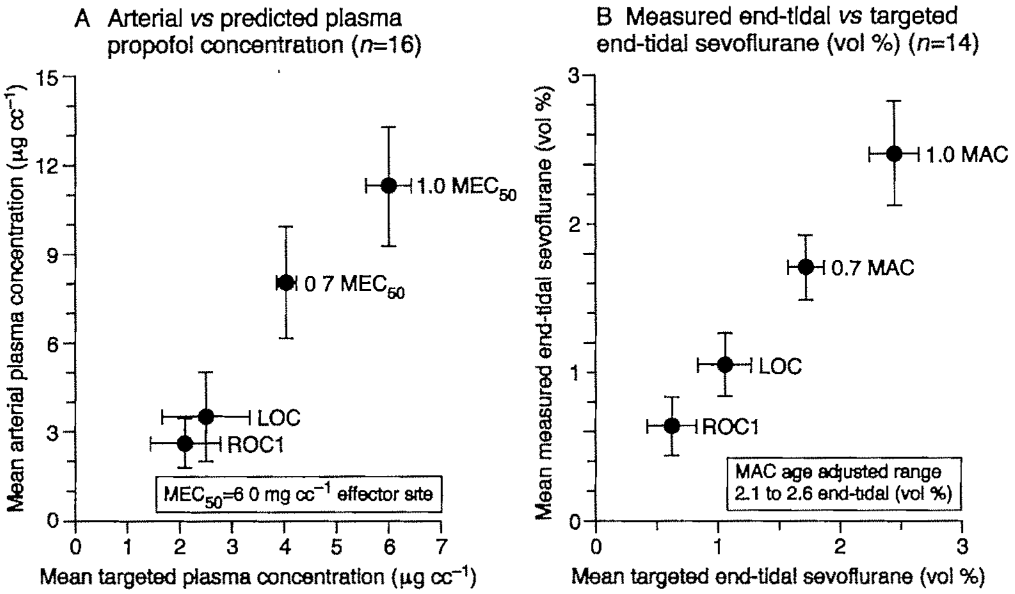

Fig. 1 Plots showing the relationship between mean arterial plasma propofol concentration and StanPump predicted propofol plasma concentration at LOC and ROC and at 0.7 and 1.0 MEC_{50} levels (A), and between measured end-tidal sevoflurane and target end-tidal sevoflurane at LOC, ROC and 0 7 and 1 0 MAC levels (B).

loud verbal command after either mildly or moderately painful stimulation.

Baseline QEEG and premedication effects

None of the average premedication baseline absolute power Z-scores was significantly different from the normative values obtained from the normal awake adult database described previously. Premedication with fentanyl or fentanyl plus midazolam had no significant effect upon the QEEG. None of the ANOVA F′ values comparing the baseline non-medicated with the premedicated QEEG reached statistical significance at even the 0.05 level.

QEEG and remifentanil concentration

Mean remifentanil concentrations were greater during emergence from anaesthesia than during induction (0.5 *vs* 1.75 ng ml^{-1}). This was of little consequence for the QEEG changes associated with induction and emergence described below. ANOVAs calculated at equivalent propofol/sevoflurane target concentrations but different remifentanil concentrations obtained during induction and emergence did not reach statistical significance (all P values >0.05).

QEEG changes during induction

In order to minimize drug concentration effects on the QEEG while maximizing the relationship between QEEG changes and behavioural changes in responsiveness, QEEGs were averaged across subjects relative to the LOC end-point of OAAS=0 rather than at specific drug concentrations. When QEEGs were averaged in this manner, the global patterns of absolute power changes seen during induction were the same for sevoflurane and propofol. However, the magnitude and degree of statistical significance of these effects differed, especially during light sedation (Figs 2A and C and 4A and C). Light sedation (2 pre-LOC; measured at two 0.1 MAC/MEC_{50} concentration increments before OAAS=0) resulted in increased frontal/central beta and total power. Deeper sedation (1 pre-LOC: one 0.1 MAC/MEC_{50} concentration increment before OAAS=0) resulted in further increases in frontal/central beta and delta activity, beginning in frontal regions and propagating to posterior regions. LOC (OAAS=0) was accompanied by increased frontal predominance within every frequency band for propofol and across delta, alpha and beta, but not theta, for sevoflurane. Frontal predominance in total absolute power increased as induction progressed to LOC. No differences in the QEEG changes were observed between the left and right hemispheres.

Anaesthetic-specific effects during induction

Figure 3A presents ANOVA F′ values comparing absolute power levels for the sevoflurane *vs* propofol groups at each targeted step during induction. In the deeply sedated state and at LOC, ANOVAs suggested that propofol tended to cause a greater frontal alpha predominance than did sevoflurane. Although not shown, frontal alpha predominance continued to increase with sevoflurane but not with propofol, at the higher concentrations studied after LOC (0.7 and 1.0 MAC).

QEEG changes associated with emergence

Differences between the baseline absolute power QEEG measures, the two 0.1 MAC/MEC_{50} concentration incre-

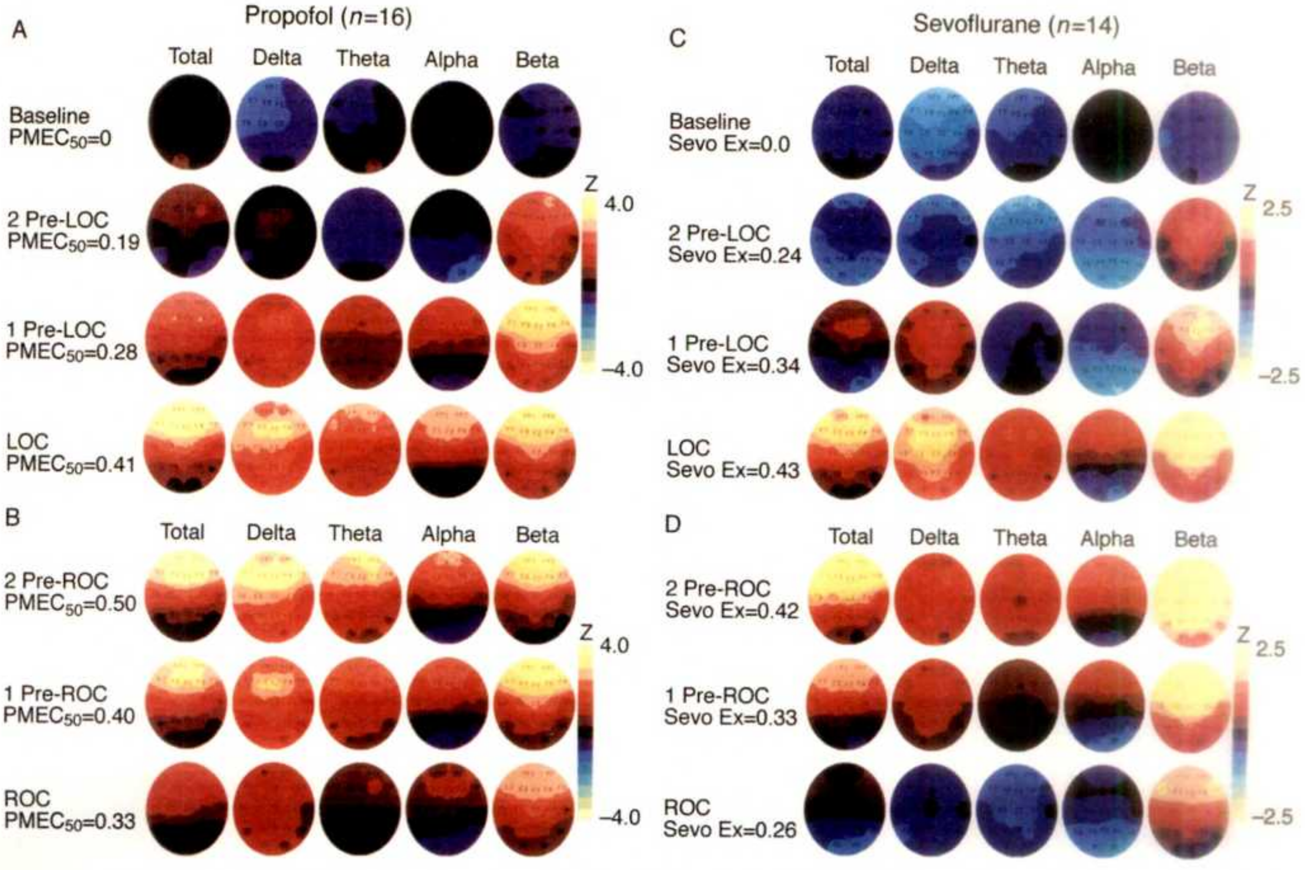

Fig. 2 Group average topographic maps of Z-transformed monopolar absolute power for the total, delta, theta, alpha and beta frequency bands. These head maps are presented separately for those volunteers who received propofol (A and B) and sevoflurane (C and D). In A and C the rows correspond to the baseline premedicated state and the two 0.1 MAC/MEC$_{50}$ concentration increments preceding and immediately after LOC. In B and D the rows correspond to the baseline premedicated state, the two 0.1 MAC/MEC$_{50}$ concentration increments preceding ROC and the 0.1 MAC/MEC$_{50}$ concentration increment immediately after ROC. All colour-coded values plotted on each head map result from interpolation across the 19 recording sites. The top of each head map represents the front of the head.

ments before ROC and at ROC are shown in Figures 2B and D and 4B and D. The pattern of QEEG changes observed during emergence is a reversal of those observed during induction. The changes were the same for sevoflurane and propofol, although once again their magnitude and degree of statistical significance differed. Frontal predominance in all frequency bands diminished as conscious awareness approached. ROC was associated with further decreases in delta and beta frontal predominance. The QEEG observed two 0.1 MAC/MEC$_{50}$ concentration increments before emergence was similar to the QEEG seen at LOC, with the exception that frontal predominance was increased. QEEG changes just before ROC also showed reduced frontal predominance, which was still prominent in beta activity. The QEEG observed at ROC resembled that seen one 0.1 MAC/MEC$_{50}$ concentration increment before LOC rather than the baseline QEEG. These QEEG changes were independent of anaesthetic concentrations as LOC (sevoflurane, 0.43 MAC; propofol, 0.41 MEC50) occurred at greater anaesthetic concentrations than did ROC (sevoflurane, 0.26 MAC; propofol, 0.33 MEC50). There were no indications of differential left *vs* right hemispheric QEEG changes associated with emergence from anaesthesia.

Anaesthetic-specific effects during emergence

Comparisons between the sevoflurane and propofol groups during emergence indicated a faster return towards baseline QEEG values for sevoflurane compared with propofol (Fig. 3B). Two 0.1 MAC/MEC$_{50}$ concentration increments before ROC, the sevoflurane volunteers showed significantly greater posterior beta absolute power, whereas the propofol group showed increased frontal delta and theta absolute power ($P<0.001$). At one 0.1 MAC/MEC$_{50}$ concentration increment before ROC, the propofol group showed greater delta, theta and alpha frontal predominance. None of these differences was observed at ROC.

Discussion

QEEG absolute power values, Z-score-transformed relative to an age-appropriate database of normal awake individuals,

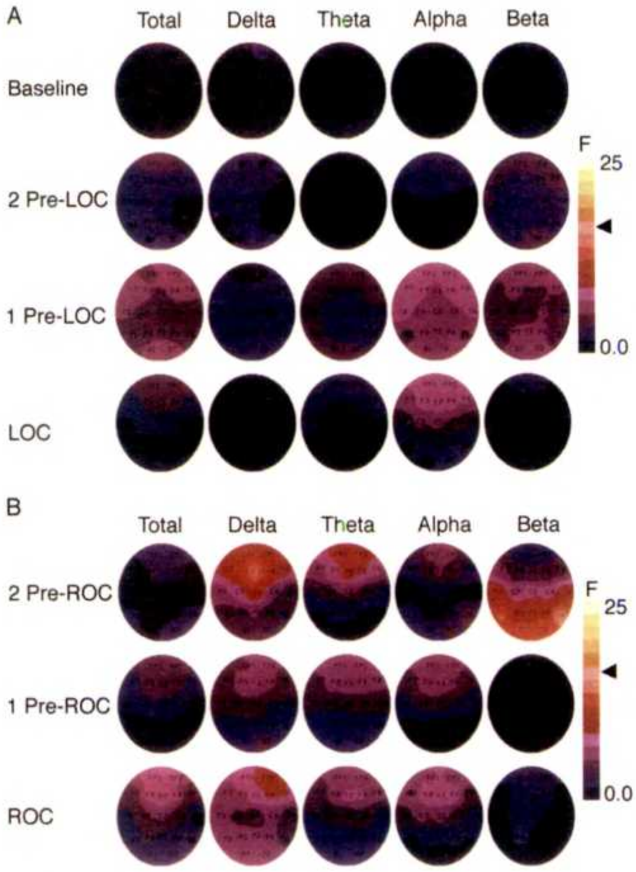

Fig. 3 Topographic maps of analysis of variance F′ values calculated on each of the 19 monopolar regions on *Z*-score absolute power values for the total, delta, theta, alpha and beta frequency bands. The rows correspond to comparisons between the propofol (A) and sevoflurane (B) groups for baseline premedicated QEEGs, the two 0.1 MAC/MEC$_{50}$ concentration increments preceding LOC, LOC, the two 0.1 MAC/MEC$_{50}$ concentration increments preceding ROC, and ROC. The F′ values calculated had 1 and 29 degrees of freedom with F′ values of 13.4 significant at the 0.001 level (see arrow on the scale).

were used to document topographic EEG changes associated with stepwise increases and decreases in anaesthetic concentration that produced the loss and return of consciousness. The QEEG technique used takes into account EEG variability due to age and pre-existing brain pathology and appropriately transforms EEG variables to meet the assumptions of parametric statistical procedures. This technique has shown high test–retest reliability[15 16] and the normal QEEG database used as a reference group has been repeatedly replicated and shown to be free of ethnic and cultural bias.[17–24] Both of these findings were confirmed in the present study. The awake, non-medicated baseline QEEG evaluations did not differ statistically from each other between the two tests on each patient, despite the fact that 1–2 months passed for each individual before testing during their second anaesthesia protocol. Further, the average QEEG values for these volunteers, all of whom had been screened for pre-existing neurological and/or psychiatric disorders, did not differ statistically from the normal adult population values. The use of this QEEG technique may explain the lack of hemispheric effects found in this study, contrary to the hemispheric EEG differences reported by Kisimoto and colleagues during propofol administration.[6] It is possible that hemispheric differences reported in their study represent patient population sampling effects.

The QEEG changes observed during induction and emergence during the propofol and sevoflurane protocols can reasonably be considered to be specific for alterations in sedation level, and substantially independent of anaesthetic type and concentration. The QEEG analyses were centred on clinically defined end-points (LOC and ROC), times that drug concentrations differed both within individuals across anaesthetics and between individuals within anaesthetics. Only QEEG changes which were common to sevoflurane and propofol administration were considered to reflect changes in arousal level. The anaesthetic-independent QEEG changes during light sedation included loss of the posterior alpha predominance seen in the normal relaxed, eyes-closed EEG, accompanied by a shift towards frontal EEG predominance. This occurred initially within the beta range, with deeper levels of sedation involving alpha activity, and at still deeper levels the delta and theta frequency bands. At LOC, frontal predominance was maximal in the alpha and beta bands and continued to increase for slow waves that also spread to more posterior regions. QEEG changes associated with light levels of sedation were equivalent for sevoflurane and propofol. Anaesthetic-specific effects were observed immediately before and at LOC. Propofol administration caused a greater increase in frontal alpha predominance at LOC than did sevoflurane. However, as sevoflurane concentrations were increased beyond those necessary to cause LOC, the differences disappeared.

Anaesthetic-independent QEEG changes associated with ROC were a gradual reversal of those which occurred at LOC, with the proviso that the QEEG and level of responsiveness measured at ROC resembles that seen before LOC rather than the awake, premedicated baseline state. This reflects the frequently made observation that patients regain conscious awareness at depressed levels of arousal, whereas just before induction they are alert and anxious, and readily respond to simple verbal commands. Emergence was preceded by a generalized decrease in delta and theta absolute power with a concurrent reduction in frontal predominance within these frequency bands. A decrease in alpha and an increase in beta frontal predominance followed. ROC was associated with a further reduction of frontal predominance that remained present in the beta frequency band only. Anaesthetic-specific QEEG changes associated with ROC were similar but opposite to the anaesthetic-specific effects present at LOC. The loss of power in the delta and theta bands and the subsequent decrease and loss of frontal predominance in all bands

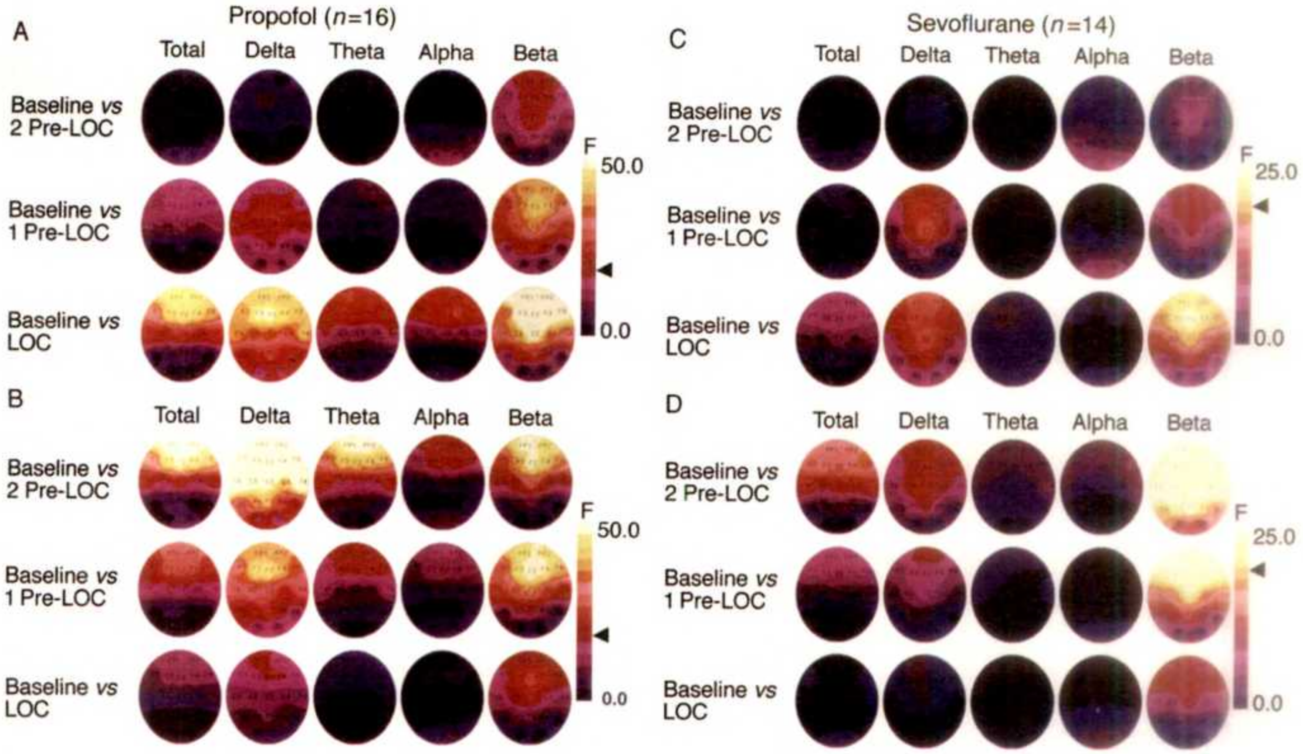

Fig. 4 Topographic maps of analysis of variance F′ values calculated on each of the 19 monopolar regions on Z-score absolute power values for the total, delta, theta, alpha and beta frequency bands. These head maps are presented separately for those volunteers who received propofol (A and B) and sevoflurane (C and D). In A and C the rows correspond to comparisons between the baseline premedicated measures, the two 0.1 MAC/MEC$_{50}$ concentration increments preceding LOC and the 0.1 MAC/MEC$_{50}$ concentration increment immediately after LOC. The F′ values have 1 and 15 (propofol) and 1 and 13 (sevoflurane) degrees of freedom, with F′ values of 16.6 (propofol) and 17.8 (sevoflurane) significant at the 0.001 level (see arrow on the scales of F values). In B and D the rows correspond to comparisons between the baseline premedicated measures, the two 0.1 MAC/MEC$_{50}$ concentration increments preceding ROC and the 0.1 MAC/MEC$_{50}$ concentration increment immediately after ROC. All colour-coded values plotted on each headmap are equivalent to those described for Fig. 2.

occurred to a greater extent with sevoflurane before ROC than it did with propofol. It should be noted that both the magnitude and the statistical significance of the anaesthetic-independent effects shown in Fig. 4 (change as a function of OAAS score) are two to four times greater than the anaesthetic-specific effects shown in Fig. 3 (change as a function of anaesthetic type).

Similar and reversible LOC/ROC QEEG changes occurred despite the fact that remifentanil concentrations were greater during the recovery from anaesthesia than during induction, as defined in the protocols used. Remifentanil concentration had minimal effect upon the QEEG despite the possible influence of remifentanil concentration upon the propofol and sevoflurane concentration differences observed between LOC and ROC. These concentration differences may also be explained by a hysteresis effect.[25]

The finding that invariant QEEG changes occur during induction and emergence from two different anaesthetic regimens supports the notion that QEEG can be used to monitor anaesthetic delivery. Indeed, there are several systems currently available on the market for this purpose. The current research findings have implications for determining the types of QEEG features that may be important for use in an anaesthesia monitoring system. Further, the topographic nature of the invariant QEEG changes observed suggests that anterior/posterior EEG recording derivations may be important to optimize the sensitivity of such a device.

Knowledge about the generators of each EEG frequency band can provide information relevant to the development of hypotheses about the neuroanatomical, neurophysiological and neurochemical mechanisms underlying the sedative and hypnotic effects shared by sevoflurane and propofol. The EEG power spectrum is mediated by an anatomically complex and diverse system that involves brainstem, thalamic, hippocampal and cortical/cortical neuronal pathways that use all known neurotransmitters. Specific portions of this system are involved in the generation of EEG within each frequency band, the interaction of activity among these generators being responsible for the frequency distribution of the EEG.[22 26 27] Both propofol and sevoflurane anaesthesia would appear to affect each of these systems. As sedation levels increase, the posterior regions show a decrease in alpha activity, and an initial excitation of the frontal cortical regions becomes manifest. With deepening levels of sedation, the prominence of the frontal changes increases from midline frontal to frontal/polar regions. With loss of consciousness, slow-wave activity (delta and/or theta) becomes more prominent, with a simultaneous decrease in alpha and beta activity. This may represent a decrease in cortical/cortical generator activity, with a shift towards control by the thalamocortical and hippocampal/septal generators of delta and theta activity. The return of consciousness is associated with a reversal of these effects. A more detailed exposition of the neurophysiology of consciousness and its relationship to QEEG has been published recently.[28] While the above descriptions are speculative, they may serve to highlight the importance of further study of the neurophysiological mechanisms involved in the generation of the EEG to help identify the common and unique mechanisms affected by various sedative and hypnotic agents.

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Erythropoietin therapy and preoperative autologous blood donation in children undergoing open heart surgery

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We assessed the feasibility and efficacy of subcutaneous erythropoietin alpha (EPO) therapy and preoperative autologous blood donation (ABD) in children undergoing open heart surgery. Thirty-nine children were treated consecutively with EPO (100 U kg^{-1} s.c. three times a week in the 3 weeks preceding the operation and i.v. on the day of surgery) and two ABDs were made (Group 1). As controls to compare transfusion requirements, 39 consecutive age-matched patients who had undergone open heart surgery during the two preceding years were selected (Group 2). In a mean time of 20 (SD 5) days, 96% of scheduled ABDs were performed and only three mild vasovagal reactions were observed. The mean volume of autologous red blood cells (RBC) collected was 6 (1) ml kg^{-1} and the mean volume of autologous RBC produced as a result of EPO therapy before surgery was 7 (3) ml kg^{-1}, corresponding to a 28 (11)% increase in circulating RBC volume. The mean volume of autologous RBC collected was not different from that produced [6 (1) *vs* 7 (3) ml kg^{-1}, P=0.4]. Allogenic blood was administered to three out of 39 children in Group 1 (7.7%) and to 24 out of 39 (61.5%) in Group 2. Treatment with subcutaneous EPO increases the amount of autologous blood that can be collected and minimizes allogenic blood exposure in children undergoing open heart surgery.

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Concerns raised by the risks that are associated with receiving allogenic blood transfusion have made preoperative autologous blood donation (ABD) a useful adjunct in elective surgery.[1 2] It reduces the risks of exposure to allogenic blood and is accepted by most physicians as the safest blood component.

Great efforts have been made in recent years to develop blood-saving techniques so that open heart surgery can be performed without allogenic blood transfusion.[3] This goal is more difficult to achieve in children. They often have iron deficiency anaemia, which is made worse by repeated blood sampling. Moreover, their blood is diluted to a greater extent than in adults by extracorporeal circulation. Blood transfusion is therefore more frequent in children during cardiac surgery.[4] Storage of autologous blood before surgery would help to reduce exposure to allogenic blood in children.

The use of recombinant human erythropoietin alpha (EPO), the primary growth factor for red blood cells, is safe and effective in the treatment of anaemia associated with chronic renal failure, human immunodeficiency virus infection and cancer.[5] Knowledge of the scientific and physiological basis of EPO[6 7] has supported its use in patients undergoing elective surgery. As a result, EPO therapy has been approved in the USA, Japan, Europe and Canada for use in patients donating autologous blood before surgery.[8]

At our institution, the blood conservation programme for children undergoing open heart surgery is based on the use of intraoperative tranexamic acid, intraoperative and postoperative transfusion of shed mediastinal blood and the use of prudent transfusion guidelines.[9–11] More recently, treatment with preoperative subcutaneous EPO to facilitate ABD has been adopted. This study was performed to assess the

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Table 1 Characteristics of children treated with EPO and ABD before operation (Group 1) and controls (Group 2). Where applicable, data are shown as mean (standard deviation) (range) AVC=atrioventricular canal, VSD=ventricular septal defect, ASD=atrial septal defect

	Group 1	Group 2	*P*
Male/female (*n*)	26/13	20/19	0.25
Diagnosis (*n*)	1 AVC/3 VSD/35 ASD	5 VSD/34 ASD	
Age (yr)	6.3 (3.1) (2–14)	6.6 (3.3) (2–14)	0.68
Body weight (kg)	22.2 (8.9) (12–40)	23.6 (11) (12–53)	0.54
Total blood volume (ml)	1551 (621) (900–3000)	1652 (760) (840–3710)	0.52
Cardiopulmonary bypass time (min)	40 (36) (14–176)	31 (15) (17–84)	0.15
Aortic cross-clamp time (min)	22 (21) (5–108)	17 (9) (7–54)	0.18

feasibility and efficacy of such treatment and its effect on allogenic blood transfusion in children undergoing open heart surgery.

Material and methods

Between January 1997 and June 1999, 39 consecutive paediatric patients were managed with EPO and ABD (Group 1). Inclusion criteria were: elective open heart surgery for atrial and/or ventricular septal heart defect; a pretreatment haemoglobin concentration between 10 and 14 g dl^{-1}; good haemodynamic status (NYHA class I or II); no concomitant infections or haematological disease; and suitable venous access. This study was approved by the ethics committee of our hospital and written informed consent was obtained from the parents.

Group 1 children received EPO (Eprex, Janssen-Cilag, High Wycombe, UK) 100 U kg^{-1} s.c. three times a week during the 3 weeks preceding the operation and 100 U kg^{-1} i.v. on the day of surgery, to a total dose of 1000 U kg^{-1}. Oral iron sulphate supplementation was given (60 mg day^{-1}) during the 3 weeks preceding the operation and during the entire hospital stay. Blood for the first and second ABDs was collected 3 and 2 weeks preoperatively respectively, provided that the haematocrit exceeded 33%.

Phlebotomies were performed by the anaesthetist on an outpatient basis. The patients underwent cardiac monitoring (pulse oximetry, blood pressure, ECG) during the procedure. An 18-gauge needle was inserted in the antecubital vein of the arm and connected to the collection bag by a three-way tap to allow infusion of small boluses of saline to prevent needle occlusion. At each phlebotomy, blood (9 ml kg^{-1}) was drawn and saline was then infused for volume replacement. The blood was collected in a single 450 ml bag containing 14 ml anticoagulant solution per 100 ml of whole blood (CPDA-1) and stored by the blood transfusion service. The maximum length of storage was 35 days.

As a control for the transfusion requirement, 39 consecutive age-matched patients who had undergone open heart surgery for atrial and/or septal defect at our institution between July 1995 and December 1997 were selected (Group 2). During this 4-yr period, all the children were followed by the same surgical and anaesthetic team and underwent the same blood conservation programme.

For all the children, cardiopulmonary bypass (CPB) was performed using a membrane oxygenator with a prime volume of 700 ml for a body weight of less than 25 kg (Lilliput 2, Dideco D 902, Dideco, Mirandola, Italy) or 900 ml for a body weight more than 26 kg (Midiflo, Dideco D 705). Myocardial protection was performed with a cold, intermittent hyperkalaemic infusion. Tranexamic acid (10 mg kg^{-1}) was given before bypass followed by continuous infusion at 2 mg kg^{-1} h^{-1} to prevent fibrinolysis.

Our blood conservation protocol included the use of a cell-saving device (Compact A, Dideco). Depending on the patient's haematocrit, the blood remaining in the circuit was returned to the patient as whole blood, directly or after ultrafiltration, or as red blood cell (RBC) concentrate, after washing and concentration in the cell-saving system. Postoperative shed mediastinal reinfusion was performed if 300 ml autologous blood or more was present in the containers at 3 and 6 h.

The decision to give blood was based on each patient's clinical condition, with a haematocrit transfusion trigger of 18% during CPB and of 26% in the intensive care unit.

The following laboratory variables were measured: RBC count, haemoglobin concentration, haematocrit, white blood cell count and platelet count. In Group 1, blood samples were drawn before the beginning of EPO therapy; before the second ABD; immediately before surgery; after surgery; and on postoperative days 1 (POD1) and 7 (POD7). In Group 2, these variables were taken from clinical records, but only the preoperative values, the postoperative values and the values on POD1 were always available.

Despite erythropoietin treatment, RBC counts usually decreased during the period of ABD in Group 1. Preoperative autologous RBC production in these patients was therefore estimated from the total volume of RBC collected minus the change in circulating RBC between the first donation and the day of surgery.[12] (In the few patients in whom the RBC count increased during this period, the increase was added to the volume of RBC donated.) The volume of autologous RBC collected at each phlebotomy was determined by multiplying the peripheral venous haematocrit by the volume of blood drawn. Circulating RBC volume was determined by multiplying the patient's

Table 2 Details of preoperative autologous donation in children treated with EPO and ABD before operation (Group 1) Where applicable, data are shown as mean (standard deviation)

ABD variables	Group 1
Number scheduled/number performed	78/75
Collection time before surgery (days)	20 (5)
Whole blood collected (ml/patient)	366 (121)
Whole blood collected (ml kg^{-1})	17 (3)
RBC volume collected (ml kg^{-1})	6 (1)
RBC volume produced (ml kg^{-1})	7 (3)

Table 3 Perioperative blood conservation measures and RBC loss in children undergoing elective open heart surgery. children treated with EPO and ABD before operation (Group 1) and retrospective controls (Group 2). Where applicable, data are shown as mean (standard deviation)

	Group 1 (*n*=39)	Group 2 (*n*=39)	*P*
Number receiving blood remaining in CPB circuit	25	28	0.63
Intraoperative shed mediastinal blood reinfused	14	7	0.13
Total intraoperative blood salvaged (ml)	249 (49)	258 (170)	0.75
12 h chest tube drainage (ml)	157 (105)	253 (193)	0.008
Postoperative shed mediastinal reinfusion (*n*)	0	1	
Perioperative RBC loss (ml kg^{-1})	11.4 (7.2)	13 (8.6)	0.38

total blood volume by the body haematocrit. Total blood volume was determined by multiplying body weight in kilograms by 75 ml kg^{-1},[13] and was assumed not to change during the period of treatment. Body haematocrit was determined by multiplying the peripheral venous haematocrit by 0.91.[14]

The perioperative RBC loss was estimated from the difference in circulating RBC on the day of surgery and the first postoperative day, plus the RBCs transfused in the same period. A standard unit of allogenic packed RBC was considered to contain 200 ml of RBC[15] and the amount of allogenic RBC transfused was therefore determined by multiplying the number of allogenic RBC units transfused by 200.

Statistical analysis

Differences between the two groups were analysed by two-tailed Student's *t*-test for unpaired data. Intragroup analysis was performed by means of two-tailed Student's *t*-test for paired data, when indicated. Proportions were compared with the two-sided Fisher exact test or the χ^2 test, as indicated. Differences were considered to be significant if the *P* value was less than 0.05. All values are expressed as mean (standard deviation) unless specified otherwise.

Results

Patient characteristics are shown in Table 1. The two groups were similar with regard to physical characteristics, blood volume and surgical operating time (Table 1). Age was 6.3 (SD 3.1) (range 2–14) and 6.6 (3.3) (2–14) yr in Groups 1 and 2 respectively. In Group 1 subcutaneous EPO injections were well tolerated without adverse systemic or local reactions. Seventy-five per cent of the 78 scheduled ABD collections (96%) were performed over 20 (5) days. The second ABD was not performed in three patients because they were living a long way from the hospital (two cases) or because of inadequate venous access (one case). Donations were well tolerated, with the exception of three mild vasovagal reactions. Each procedure was performed in 1 h, between the arrival of the patient and discharge from the hospital.

Data on the collection and production of autologous RBC are shown in Table 2. The mean volume of whole blood donated was 17 (3) ml kg^{-1}, which corresponds to 6 (1) ml kg^{-1} RBC volume. Mean preoperative autologous RBC production was 7 (3) ml kg^{-1}, an increase of 28 (11)% over the circulating RBC volume at baseline. The volume of RBC collected was not different from that produced [6 (1) *vs* 7 (3) ml kg^{-1}, *P*=0.4]. The mean volume of autologous units was 183 (60) (range 90–300) ml, corresponding to a mean RBC volume per autologous unit of 68 (25) (35–122) ml.

All children had an uncomplicated perioperative course and were extubated within 8 h after surgery. In one patient in Group 1, a second period of CPB was required for the repair of left atrioventricular valve stenosis. In one patient in Group 2, reopening was necessary 3 h after surgery because of mediastinal bleeding. No statistically significant differences were found between the two groups with regard to recovery of blood remaining in the CPB circuit, intraoperative shed mediastinal blood reinfusion or total intraoperative blood salvage (Table 3).

Mean perioperative RBC loss was similar in Group 1 and Group 2 (11.4 (7.2) and 13 (8.6) ml kg^{-1} respectively; *P*=0.38) (Table 3).

Chest tube drainage was significantly reduced during the first 12 h after surgery in Group 1 compared with Group 2 patients (7.8 (4.8) and 12 (8.7) ml kg^{-1} respectively; *P*=0.01). In one case in Group 2, chest tube drainage exceeded 100 ml for three consecutive hours and the blood was transfused (Table 3). There were no perioperative deaths and all children were discharged from hospital well. The length of hospital stay was 6.7 (0.8) and 6.4 (0.9) days in Group 1 and Group 2 respectively (*P*=0.12).

In Group 1, the pretreatment and preoperative haemoglobin concentrations were similar (Table 4). The haemoglobin concentration fell after surgery from 12.4 (1.4) to 10 (1.6) g dl^{-1}; it was 10.9 (1.4) g dl^{-1} after discharge from the intensive care unit on POD1 and it remained unchanged during the subsequent 7 days. The preoperative platelet count in Group 1 increased significantly during the treatment period, from 245×10^3 (61×10^3) to 326×10^3 (95×10^3) ml^{-1} preoperatively, decreased after surgery to 188×10^3 (52×10^3) ml^{-1} and returned to the pretreatment value within a week after the operation (Table 4).

Table 4 Haemoglobin concentration (Hb) and platelet count before and after open-heart surgery in children treated with EPO and ABD before operation (Group 1) and in controls (Group 2). Where applicable, data are shown as mean (standard deviation) **P*=0.15 *vs* preoperative, intragroup, not significant. †*P*=0.22 *vs* POD7, intragroup, not significant †*P*<0 001 *vs* preoperative, intragroup. §*P*=0 01 *vs* POD7, intragroup

	Group 1	Group 2	*P*
Pretreatment Hb (g dl^{-1})	12.2 (0.9)*		
Preoperative Hb (g dl^{-1})	12.4 (1 4)	12.7 (0 9)	*P*=0 26
CPB Hb (g dl^{-1})	7 2 (1.1)	7 7 (0.9)	*P*=0.03
Postoperative Hb (g dl^{-1})	10 (1 6)	10.8 (1.6)	*P*=0.03
Hb (g dl^{-1}) on POD1	10 9 (1 4)†	10 9 (1 5)	*P*=1 00
Hb (g dl^{-1}) on POD7	11 1 (1.5)		
Pretreatment platelets (10^3 ml^{-1})	245 (61)‡		
Preoperative platelets (10^3 ml^{-1})	326 (95)	264 (51)	*P*<0.0001
Postoperative platelets (10^3 ml^{-1})	188 (52)	172 (46)	*P*=0 15
Platelets (10^3 ml^{-1}) on POD1	212 (57)§	193 (43)	*P*=0 10
Platelets (10^3 ml^{-1}) on POD7	231 (62)		

In Group 2, the preoperative haemoglobin concentration was similar to that observed in Group 1 (Table 4). The haemoglobin concentrations in Group 2 were higher during CPB and postoperatively than those in Group 1 (*P*=0.03), while the concentrations on POD1 were similar (Table 4). The preoperative platelet count was significantly lower in Group 2 than in Group 1 and the postoperative and POD1 platelet counts were slightly reduced, although not significantly (Table 4).

Children in Group 1 received all the ABD collected during the operative or the postoperative period. Three of the 39 children (7.7%) required allogenic blood during surgery: one patient required 1 unit, a second patient required 2 units and the third patient 3 units. Only one of these children needed fresh frozen plasma and none of them needed platelet transfusion.

A total of 33 units of allogenic packed RBC was administered to 24 out of 39 (61.5%) children in Group 2 during the operative or postoperative period. Eighteen of the 24 patients (75%) required 1 unit of packed RBC, four patients required 2 units and two patients required 3 and 4 units respectively. In addition, four of these children needed fresh frozen plasma but no patient needed platelet transfusion. In the control group, allogenic blood transfusion was needed during CPB in 13 out of 39 children (33%).

Discussion

Although allogenic blood is safer than ever, the reasons for avoiding blood transfusion remain valid, including the preservation of a limited resource.[16] During open heart surgery, allogenic blood transfusion is frequently required. Consequently, great efforts have been made in recent years to develop blood-saving techniques and treatments to allow open heart surgery to be performed without blood transfusion.[3] However, it is more difficult to avoid allogenic blood transfusion in children undergoing open heart surgery, particularly because their blood is diluted to a great extent during CPB.[4] Although allogenic blood transfusion in children undergoing open heart surgery has declined dramatically over the last three decades, the number of patients still exposed to it remains high.[4 17–19] In the present study, one in every three transfused patients in the control group needed allogenic blood during CPB because of blood dilution. Most of these patients needed 1 standard unit of allogenic packed RBC. Because 1 standard unit of packed RBC contains 200 ml of RBC, this strongly suggests that most of these children could have avoided transfusion of allogenic blood if they had donated at least 2 units of autologous blood.

This study assessed the feasibility and safety of preoperative EPO and ABD, its effectiveness in augmenting autologous RBC count and its effect on allogenic blood transfusion in children undergoing open heart surgery. Complications of blood donation, including syncope, has been described in 2–5% of healthy blood donors.[20] Although the consequences of such events could have been more serious in patients with cardiovascular disease, the risk of autologous blood donation is probably overestimated. In a report of autologous donation in patients awaiting heart transplantation, the haemodynamic effects of ABD were not different from those observed in a control population without cardiac disease.[21] Available data indicate that ABD is safe and feasible and can be used for children of a wide range of age and weight and in a variety of surgical procedures.[22–25] Although venous access may be more difficult preoperatively, the benefits of avoiding allogenic blood transfusion are greater in children because of their longer life expectancy, as the possible consequences of blood-borne infections are more serious and long-lasting in younger patients.

In the present study, donations were well tolerated, with only a low incidence of vasovagal reactions (4%). In addition, 96% of the scheduled collections were performed and none cancelled because of refusal by the children or their parents.

The safety of EPO therapy in patients undergoing elective surgery has been demonstrated in more than 1000 patients in placebo-controlled trials.[8] Thrombotic events described in patients with chronic renal failure have not been seen with EPO therapy in the surgical setting.[26] In our series we did not observe any side-effects of EPO therapy, such as thrombotic events or hypertensive attacks, which is in accordance with the data available in the literature.[8] On the other hand, we observed a significant (30%) increase in platelet count from baseline during treatment in children in Group 1 (Table 4). As a result, the preoperative platelet count was significantly higher in children treated with EPO and remained higher after surgery, without the difference reaching significance compared with controls.

The effect of EPO on platelet count remains controversial. In a recent review, Beguin[27] suggested that moderate stimulation by EPO causes a moderate elevation of the platelet count. whereas intense EPO stimulation causes some degree of thrombocytopenia, probably as a result of inhibition of platelet production. The two groups of patients reported in this study were not randomized, so our observations should be taken with caution. However, if confirmed in a randomized study, our results could be of some value. In fact, a report on haemostasis in children undergoing open heart surgery found a significant inverse association between platelet count and blood loss.[17] In our experience, the perioperative blood loss was not different in the two groups, and the chest drainage after operation in patients treated with EPO was 35% less than in the control group. Though not randomized, the two groups were similar with regard to physical and operative characteristics, were followed by the same surgical and anaesthetic team and underwent the same blood conservation programme. It is tempting to speculate that the higher preoperative platelet count might be considered beneficial rather then a harmful collateral effect of EPO administration, favouring haemostasis in the immediate postoperative period.

It has been suggested that the most effective way to minimize the use of allogenic blood is the combination of preoperative EPO therapy with the procurement of autologous blood by acute normovolemic haemodilution or donation.[8] Several studies have addressed the use of EPO to facilitate ABD[28 29] and, though it is expensive, general agreement exists on its utility in anaemic autologous donors.[30] Few data have been published on the use of EPO, either alone or associated with ABD, in adult cardiac surgery. Nonetheless, EPO seems to be adequate therapy for increasing mean haemoglobin concentrations by approximately 1 g dl^{-1} per week of treatment, and is effective in allowing ABD collection and reducing exposure to allogenic blood.[31–35] Even fewer data are available on the use of EPO in paediatric cardiac surgery[4 36] and, to our knowledge, no data exist on EPO therapy associated with ABD in children.

Our protocol of s.c. administration of EPO at a total dose of 1000 U kg^{-1} during the 3 weeks preceding operation allowed the collection of 6 (1) ml kg^{-1} of autologous RBC without reduction in the haemoglobin concentration and with a net production of new autologous RBC corresponding to nearly 30% of the circulating RBC volume at baseline. This net gain in autologous RBC allowed a reduction in allogenic RBC transfusion compared with controls. The amount of autologous blood collected was generally adequate, because almost 92% of children treated with EPO and ABD received no allogenic blood.

Though effective, this treatment is expensive.[37 38] In our experience, the approximate cost of 1000 units of erythropoietin corresponds to about 10 US dollars and that of one ABD unit to about 70 US dollars. For a child weighing 20 kg, the cost of the treatment (20 000 EPO units plus 2 ABD units, manpower and indirect costs excluded) would be almost 340 US dollars. The adoption of weekly regimens with lower doses of EPO will reduce the cost.[8] Nonetheless, this treatment should be reserved for carefully considered circumstances in which the cost is offset by well-defined clinical benefits. We think that this regimen is apposite for young patients undergoing open heart surgery, in whom mild preoperative anaemia is frequent, life expectancy is long and a substantial blood requirement is expected, mainly related to haemodilution during CPB

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Changes of haemostasis in patients undergoing major abdominal surgery—is there a difference between elderly and younger patients?

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Many physiological functions are altered in the elderly. It is not clear whether this applies to haemostatic mechanisms in patients undergoing major surgery. Twenty-five consecutive patients <60 yr and 25 consecutive patients >70 yr scheduled for abdominal surgery for malignancies were included in our study. Various standard coagulation variables and specific markers of coagulation were serially measured before surgery (baseline), at arrival on the intensive care unit (ICU), 4 h after arrival on ICU, and on the morning of the first postoperative day. Platelet function was assessed using the Platelet Function Analyser PFA-100| with adenosine diphosphate (ADP) as an inductor. Anaesthesia and surgery were similar between the elderly (76(3) years) and younger (53(5) years) groups. Baseline plasma levels of prothrombin fragments F1+2, thrombin-antithrombin III (TAT) complex, and D-dimers were significantly different between the two groups, indicating thrombin activation and fibrin formation in the elderly. Postoperatively, only F1+2 plasma levels were significantly higher in the elderly (4.0(0.8) nmol/l) than in the younger patients (2.2(0.9) nmol/l), whereas the course of D-dimer and TAT did not differ significantly between the two groups. Endothelial-derived markers of coagulation (von Willebrand factor, collagen-binding activity of von Willebrand factor) were not different between the groups throughout the study period. Platelet function was impaired in the elderly compared with the younger patients. It is concluded that elderly patients showed more prothrombin activation/thrombin generation and increased fibrinolytic activity prior to surgery than younger patients. However, perioperative changes of coagulation in the elderly were similar to those seen in younger patients.

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The proportion of elderly people in the population is increasing rapidly.[1] By the year 2030, 17% of the population in the USA will be >65 yr.[2] It is generally accepted that the function of several organs is altered in the elderly and the margin of reserve for adaptation is reduced.[3] A deterioration in pulmonary, renal, and cardiovascular function is well documented.[4–6] Secondary to the high incidence of co-existing diseases elderly patients are at increased risk of developing postoperative complications.[1] Age-specific alterations of organ function appear to predispose to the development of postoperative multiorgan failure.[7] [8] The coagulation system may also be affected by ageing. [9] Imbalances in haemostasis are commonly seen in the surgical patient either due to extensive blood loss, hypothermia or activation of inflammatory pathways with subsequent activation of procoagulatory mechanisms and down-regulation of anticoagulant pathways. Even moderate surgical trauma (e.g. reduction mammoplasty) was shown to activate thrombin generation and fibrinolysis.[10] More severe alterations of the haemostatic process are expected in patients undergoing complex, long-lasting surgical procedures. The development of sensitive immunochemical methods enables us to increase our understanding of the coagulation process. Since the influence of advanced age on

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coagulation in the surgical patient is not well defined, this observational study was designed to assess whether haemostasis differs between elderly and younger patients undergoing major abdominal surgery. For this purpose, various aspects of the coagulation process were serially measured: thrombin generation/thrombin neutralization, fibrin formation/degradation, endothelial-related coagulation, and platelet function.

Methods

The study was performed according to the guidelines of the Institutional Review Board of the hospital. Before the patients were included into the study, written informed consent was obtained from each patient. Twenty-five consecutive elderly (>70 yr) and 25 younger patients (<60 yr) scheduled for major abdominal surgery for malignancies were studied. Patients with preoperative coagulation abnormalities (activated partial thromboplastin time [aPTT] >70 s, fibrinogen <1.5 g dl $^{-1}$, antithrombin III [AT III] <40%), patients showing perioperative renal insuffiency (plasma creatinine concentration >2 mg dl^{-1}), liver dysfunction (alanine transferase/aspartate aminotransferase >40 U litre^{-1}), diabetes mellitus, or valvular heart disorders were excluded from the study. Patients taking corticosteroids, aspirin, cyclooxygenase inhibitors or other non-steroidal anti-inflammatory agents were not included.

All patients received premedication with lorazepam 1 to 2 mg. Anaesthesia was induced by weight-related doses of thiopental, sufentanil, and atracurium. Anaesthesia was maintained by giving sufentanil, atracurium and isoflurane according to the patients' need. The lungs of all patients were mechanically ventilated with 60% nitrous oxide in oxygen to keep Sa_{O_2} >95% (continuous oximetry). Ventilation patterns were adjusted to keep end-expiratory carbon dioxide between 35 and 40 mm Hg (continuous capnography). After surgery all patients were transferred to the intensive care unit (ICU). On ICU, ventilation was continued if the body temperature was <36°C, gas exchange was insufficient or if there was haemodynamic instability. Regional anaesthesia was not used in the patients. The entire perioperative management was carried out by physicians who were not involved in the study.

Heart rate, mean arterial blood pressure, and central venous pressure (CVP) were measured continuously in all patients. The CVP was maintained between 12 and 14 mm Hg using crystalloid and/or gelatin infusions. Packed red blood cells were administered when the haemoglobin concentration was <9 g dl $^{-1}$. Crystalloids were administered to compensate for fluid loss by sweating, gastric tubes, and urine output or as a solvent for drugs (e.g. antibiotics). During surgery, 500 ml h^{-1} of crystalloids were given routinely in all patients. When the mean arterial pressure was <60 mm Hg despite sufficient volume therapy, dopamine was given followed by epinephrine if the mean arterial pressure was still <60 mm Hg.

From arterial blood samples standard coagulation variables (AT III, fibrinogen, platelet count and aPTT) were measured using routine laboratory tests. Additionally, D-dimer (turbidimetric method, Roche Diagnostics, Mannheim, Germany; <0.5 ng litre^{-1}), prothrombin fragments F1+2 (commercially available solid-phase enzyme-linked immonosorbent assay kit [ELISA], Dade-Behring, Marburg, Germany; normal values from healthy volunteers: 0.4–1.0 nmol litre $^{-1}$), thrombin/antithrombin III complex (TAT; using commercially available ELISA, Dade-Behring, Marburg, Germany; normal values from healthy volunteers: 1.0–4.0 μg litre^{-1}), factor VIII activity (one-stage clotting assay; Roche Diagnostics, Mannheim, Germany; normal values from healthy volunteers: 60–150 U ml^{-1}), von Willebrand factor antigen (vWF-Ag; turbidimetric method, Roche Diagnostics, Mannheim, Germany; normal values from healthy volunteers: 60–160 U dl^{-1}), collagen-binding activity of von Willebrand factor (vWF:CBA; by sandwich ELISA, Immuno-Diagnostika, Heidelberg, Germany; normal values from healthy volunteers: 0.6–1.8 U ml $^{-1}$) were measured from the same arterial blood samples. Platelet volume was measured using Coulter counter STKS (Coultronics, Margency, France). Platelet function was assessed by the Platelet Function Analyser PFA-100™ (Dade-Behring, Marburg, Germany) using adenosine diphosphate (ADP) as inductor. The time required for the platelet plug to occlude the aperture is the 'closure time' and is indicative for platelet function.[11] [12] The normal range for the PFA-100™ test using ADP in healthy volunteers has been determined to be 77–133 s. [11] All analyses were performed in duplicate by a single operator according to the instructions of the manufacturer. Measurements were performed after induction of surgery (before surgery, defined as 'baseline' value; T0), at arrival on ICU (T1), 4 h after arrival on ICU (T3), and on the morning of the first postoperative day (T4).

Statistics

We decided that a 40% change of prothrombin fragment F1+2 from baseline values would reflect abnormal changes in coagulation. The appropriate standard deviation (SD) of F1+2 has been found to be 0.4 nmol litre^{-1}.[10] For a study with a power of 0.8, a minimum of 20 patients in each group would be required to detect a difference in F1+2 at the 0.05 level.[13] Statistical analysis has been carried out using a SPSS/PC+ software (V4.0 SPSS, Inc., Chicago, USA). Data are presented as mean (SD), unless otherwise indicated. Two-way analysis of variance for repeated measurements (ANOVA) followed by post hoc Scheffé's test on the matrix of pairwise comparison probabilities was used for all serially measured variables. *P* values <0.05 were considered significant. Other variables were analysed by one-way analysis of variance (for normally distributed) and Kruskall-

Table 1 Patients' characteristics and data from the perioperative period *$P<0.05$ different to the other group

	<60 years (*n*=25)	>70 years (*n*=25)
Age (years [range])	53 (5) [36–59]	76 (3) [70–85]
Weight (kg)	70 (7)	72 (8)
Height (cm)	169 (10)	165 (8)
Gender (f/m)	12/13	14/11
ASA (II/III/IV)	18/7/0	15/9/1
Type of surgery		
rectum resection	7	9
gastrectomy	6	7
Whipple's procedure	4	3
oesophageal surgery	4	3
pancreatic resection	4	3
Duration of anaesthesia (min)	243 (32)	239 (45)
Duration of surgery (min)	212 (41)	206 (46)
Total blood loss up to first postoperative day (ml)	910 (320)	1190 (310)
Stay on ICU (days)	3.4 (1.1)	5.5 (2.5)*
Ventilation continued	11	6*
Survivors	23	22
Use of		
dopamine (no. of patients)	5	11*
epinephrine (no of patients)	2	3

Wallis one-way analysis of variance of ranks (when data were not normally distributed data). Chi-square test and Mann-Whitney U test was additionally used when appropriate.

Results

Duration of anaesthesia and the type of surgery were similar in the two groups (Table 1). The duration of stay on the ICU was significantly longer in the elderly than in the younger patients (3.4 (1.1) *vs* 5.5 (2.5) days) (Table 1). The blood loss up to the first postoperative day was not significantly different between the groups (Table 2). The volume of blood products and other intravenous fluids (Table 2) as well as haemodynamic variables (Table 3) were similar between the groups throughout the entire study period. No platelet concentrates or fibrinogen were given.

At baseline, the haemoglobin concentration was significantly lower in the elderly than in the younger patients (Table 3). From normal baseline values, fibrinogen plasma levels decreased similarly in both groups (Table 3). AT III

Table 2 Cumulative use of blood and crystalloids/colloids. PRBC, packed red blood cells, FFP, fresh frozen plasma; +$P<0.05$ different from the other group

		T0 Baseline on ICU	T1 Arrival ICU	T2 4 h	T3 First postoperative day
Gelatin (ml) (cumulative)	<60 years	–	1650 (290)	2010 (350)	2350 (350)
	>70 years	–	1550 (310)	2150 (450)	2300 (400)
Crystalloids (ml) (cumulative)	<60 years	1080 (310)	2500 (910)	4300 (950)	5200 (960)
	>70 years	980 (300)	2690 (950)	4700 (850)	5150 (860)
PRBC (cumulative) (total number of units/group)	<60 years	–	13	16	20
	>70 years	–	15	20	22
FFP (cumulative) (total number of units/group)	<60 years	–	8	10	10
	>70 years	–	10	12	12

Table 3 Haemodynamic variables and standard coagulation variables in the two groups +$P<0.05$ different to the other group, *$P<0.05$ different from baseline values

		T0 Baseline	T1 Arrival on ICU	T2 4 h ICU	T3 First postoperative day
Mean arterial pressure (mm Hg)	<60 years	91 (7)	85 (11)	86 (9)	88 (8)
	>70 years	90 (7)	88 (8)	81 (8)	81 (10)
CVP (mm Hg)	<60 years	8 (3)	12 (2)	13 (2)	12 (3)
	>70 years	7 (4)	13 (3)	12 (4)	12 (2)
Heart rate (beat min^{-1})	<60 years	79 (11)	75 (10)	84 (9)	86 (9)
	>70 years	82 (9)	77 (9)	86 (7)	88 (8)
Haemoglobin (g dl^{-1})	<60 years	13.2 (0.6)+	9.9 (0.9)	10.8 (1.4)	10.5 (1.0)
	>70 years	11.1 (0.5)	9.5 (0.7)	10.3 (1.2)	10.7 (0.9)
aPTT (normal: 25–40 s)	<60 years	34.4 (3.9)	37.6 (3.9)	35.4 (3.8)	38.6 (4.1)
	>70 years	33.1 (3.5)	40.3 (3.8)	38.7 (4.3)	41.1 (4.3)
Fibrinogen (normal. 150–400 mg dl^{-1})	<60 years	399 (52)	252 (39)*	335 (46)	409 (40)
	>70 years	402 (62)	259 (57)*	347 (77)	428 (47)
AT III (normal: 80–100%)	<60 years	94 (14)	59 (8)*	74 (11)*	84 (10)
	>70 years	69 (13)+	50 (9)	51 (12)*+	62 (8)+
Oesophageal temperature (°C)	<60 years	36.4 (0.3)	35.2 (0.4)	35.9 (0.3)	37.4 (0.3)
	>70 years	36.6 (0.4)	35.6 (0.5)	36.1 (0.2)	37.8 (0.4)

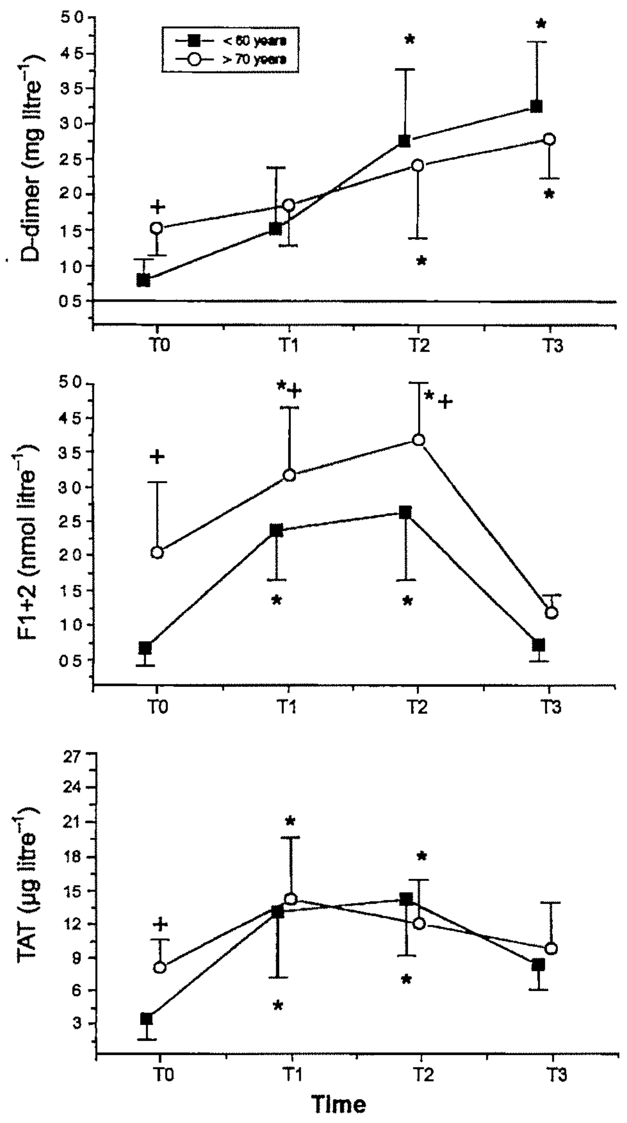

Fig 1 Changes of D-dimer (normal values: <0.5 ng litre^{-1}), F1+2 (normal values 0.4–1.0 nmol litre^{-1}), and thrombin/antithrombin III (normal values: 1.0–4.0 µg litre^{-1}) in the two groups. Mean ± SD; T0: after induction of surgery; T1: at arrival on ICU; T2: 4 h after arrival on ICU; T3: at the morning of the first postoperative day; +$P<0.05$ different to the other group; *$P<0.05$ different from baseline values.

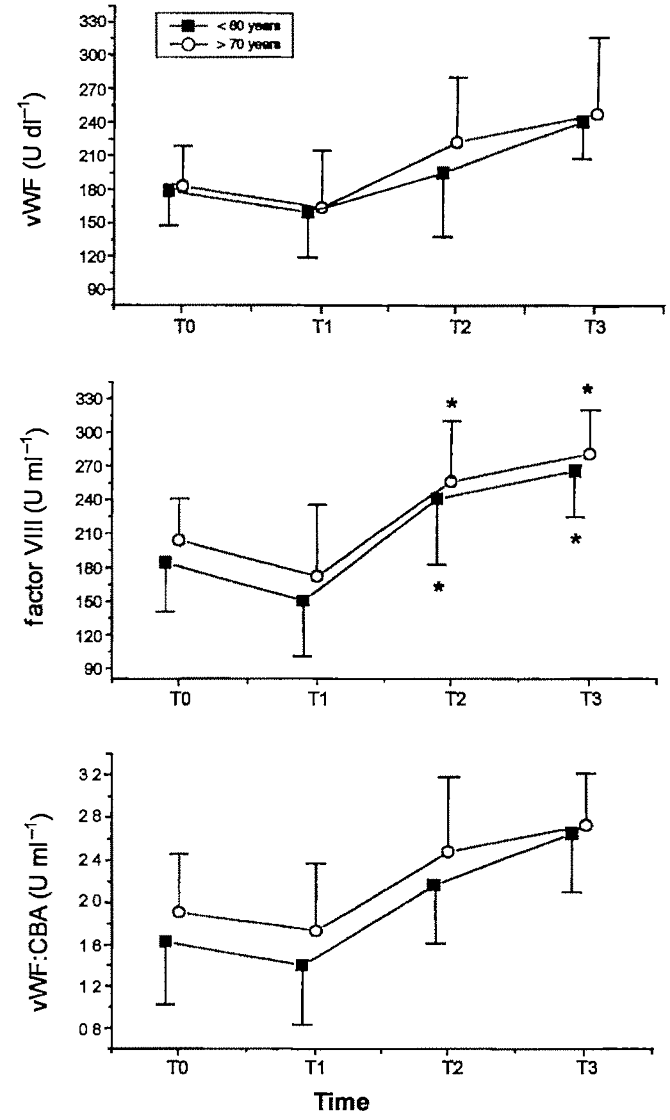

Fig 2 Changes of von Willebrand-factor antigen (normal values: 60–160 U dl^{-1}), factor VIII (normal values: 60–150 U ml^{-1}) and collagen-binding activity of von Willebrand factor (normal values 0.6–1.8 U ml^{-1}). Mean ± SD; T0: after induction of surgery; T1: at arrival on ICU; T2: 4 h after arrival on ICU; T3: at the morning of the first postoperative day; *$P<0.05$ different from baseline values.

was lower in the elderly at baseline and remained lower than in the younger patients at T2 and T3 (Table 3).

D-dimer levels were higher than normal (>0.5 ng litre^{-1}) at baseline in the elderly and significantly different compared to the younger patients (Fig. 1). D-dimer increased in both groups without the changes showing significant group differences. F1+2 plasma levels at baseline were elevated beyond normal (>2 nmol litre^{-1}) only in the elderly (Fig. 1). F1+2 increased in both groups, being significantly higher in the elderly than in the younger patients at T1 and T2. TAT plasma levels were higher than normal (>4 µg litre^{-1}) at baseline only in the elderly. TAT increased similarly in both groups (elderly: from 8.1 (1.8) to 14.6 (2.9) µg litre^{-1}; younger: from 4.9 (1.7) to 13.2 (4.5) µg litre^{-1}) (Fig. 1). vWF, factor VIII, and vWF:CAB did not differ between the two groups throughout the study period (Fig. 2).

The platelet count and platelet volume were without group differences throughout the study (Fig. 3). PFA-100 TM using ADP revealed a significantly longer closing time at baseline in the elderly than in the younger patients (Fig. 3). Immediately after arrival on the ICU (T1), 4 h thereafter (T2), and on the first postoperative day (T3), closing time was significantly higher in the elderly (T2: 148 (18) s) than in the younger patients (T2: 120 (15) s) indicating altered platelet function.

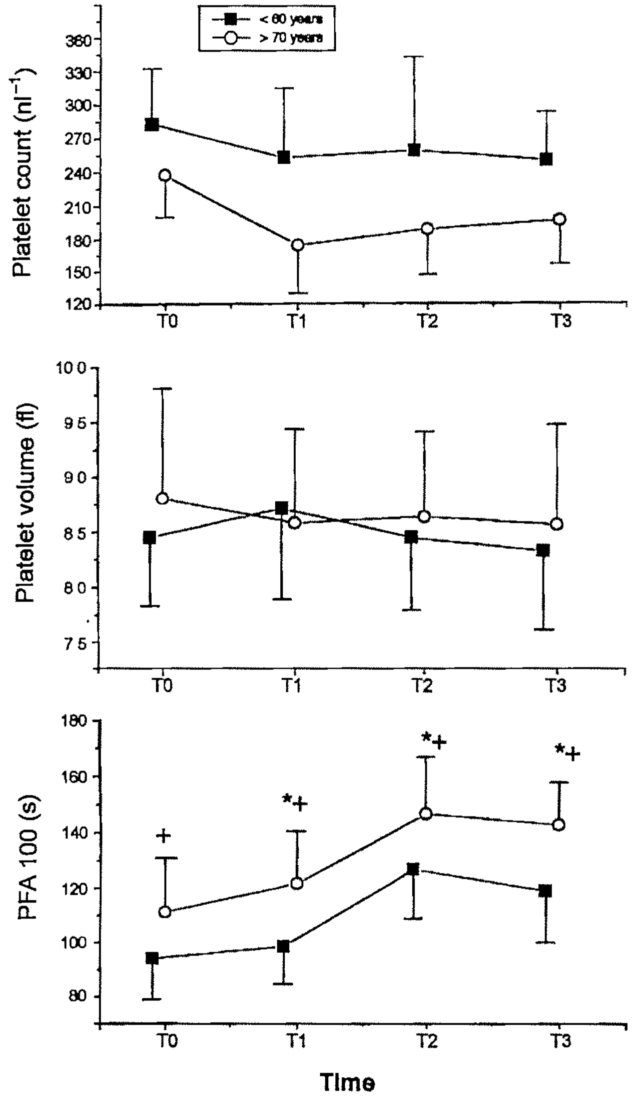

Fig 3 Changes of platelet count (normal range· 150 000 to 350 000 ml^{-1}), platelet volume (normal values· 7.8–10 fl), and closing time of the platelet factor analyser PFA-100™ using ADP as an inductor (normal values· 77–133 s) in the two groups. Mean ± SD; T0: after induction of surgery, T1: at arrival on ICU, T2: 4 h after arrival on ICU; T3: at the morning of the first postoperative day; $+P<0.05$ different to the other group; $*P<0.05$ different from baseline values.

Discussion

Surgery may cause severe modifications in haemostasis with subsequent development of a hyper- or hypocoagulable state. In addition to the surgical trauma, the neuroendocrine response and hypothermia may also impair haemostatic function resulting in decreased fibrinolysis and altered platelet activity.[14] We have included only patients undergoing abdominal surgery because it has been reported that different types of surgery were associated with varying effects on haemostasis. [15] We monitored variables that appear to be more helpful for the diagnosis of coagulation disorders than commonly used global tests. [16 17] Different aspects of haemostasis were assessed: F1+2 (a marker of thrombin generation), TAT (a marker of thrombin neutralization), D-dimer (a marker of fibrin formation and its degradation). Endothelial-related coagulation was assessed by monitoring vWF and vWF:CAB. vWF is a complex that mediates platelet adhesion to a damaged vessel wall. Platelet function was measured using the PFA-100™ that simulates coagulation close to normal haemorheological conditions.[12] The PFA-100™ uses whole blood and provides a more realistic environment to the aggregation of platelets than other tests (e.g. aggregometry). [12] When the PFA-ADP test is abnormal, the patient is likely to have a platelet defect that impairs primary haemostasis. [11 12]

One major result of our study was that elderly patients showed evidence of activated coagulation at baseline (elevated F1+2 and TAT complex) associated with increased fibrinolytic activation (elevated D-dimer) and increased inhibitor consumption (lower AT III, elevated TAT complex). Thrombin production plays a pivotal role in the development of coagulation dysfunction. Excessive thrombin generation may result in consumption of platelets and fibrinogen. Continuous activation of coagulation will result in a hypocoagulable state which is complicated by further (hyper-)fibrinolysis. At baseline, TAT and F1+2 were elevated only in our elderly patients. Both are regarded as indicators of hypercoagulability. [19] The reasons for this phenomenon can only be speculated upon: intravascular volume deficit, (occult) microcirculatory perfusion deficit, or an age-related general change in the balance between procoagulant and anticoagulant mechanisms may be possible explanations. Since liver function was normal in the elderly throughout the study period, reduced synthesis of antithrombin activity appears to be less likely. Platelet function assessed with the PFA-100™ was altered in the elderly at baseline possibly due to elevated thrombin concentration and an ongoing activation of coagulation. Hypercoagulability may be beneficial in reducing surgical bleeding, but it may also have considerable negative effects, e.g. development of venous thrombosis, pulmonary embolism or coronary artery thrombosis.[20] Tuman *et al.* found that postoperative hypercoagulability increased cardiac morbidity and affected outcome considerably in patients undergoing major vascular surgery. [21] Our study population was much too small to draw conclusions with regard to development of thrombosis, outcome or survival.

With the exception of F1+2, AT III and platelet function all other serially measured coagulation variables did not show significant differences between the elderly and younger patients during and after surgery. Measurement of F1+2 appears to be a sensitive tool for detecting accelerated thrombin generation. Thrombin generation and consecutive activation of fibrinolysis are physiological responses to tissue damage.[21] F1+2 in the elderly after surgery was moderately but significantly higher than in our younger patients.

Ongoing activation of the coagulation system may imbalance the haemostatic system and result in increased postoperative bleeding. Reduced platelet function may contribute to a disturbed coagulation process. Our data are in agreement with a study assessing the importance of molecular markers of coagulation in patients undergoing different surgical procedures showing that F1+2 was the best predictor of intraoperative haemostatic disorders, followed by D-dimer.[21]

There is a tendency to assume that the elderly patient has a worse prognosis than the younger patient because of the presence of pre-existing comorbidity with age.[3] In addition to the established age-related changes in lungs, kidneys, and cardiovascular system, there may also be differences with regard to haemostasis. This was confirmed by our data showing a moderate imbalance of the coagulation network prior to surgery. This may be of particular importance in those elderly patients who are scheduled for complex surgery and in whom complications arise postoperatively. In this situation activation of inflammatory pathways may result in additional modifications of the haemostatic network associated with the risk of bleeding or microthrombosis with subsequent development of organ failure.[22]

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Combination of external chest wall oscillation with continuous positive airway pressure

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We studied the effects of continuous positive airway pressure (CPAP) on pulmonary gas exchange during external chest wall oscillation (ECWO), and the relationship with obesity, in nine patients with normal body weight (group 'N') and 10 obese patients (group 'O'). During ECWO with CPAP 5, Pa_{CO_2} decreased in group 'O' (6.0 (SD 0.8) to 5.6 (0.5) kPa, $P<0.05$), whereas it increased in group 'N' at all levels ($P<0.01$). Arterial Po_2 ($P<0.001$) was greater and Pa_{CO_2} ($P<0.01$) less in group 'N' during CPPV and ECWO plus CPAP. We also compared the haemodynamic effects of ECWO plus CPAP with those of continuous positive pressure ventilation (CPPV). ECWO plus CPAP and CPPV were applied for 30 min to 6 ASA III patients. Cardiac output (CI 2.7 (0.5) *vs* 2.1 (0.2) litre min^{-1} m^{-2}, $P<0.05$) and stroke volume (SVI 49 (9) *vs* 32 (6) ml m^{-2}, $P<0.05$) were greater during ECWO plus CPAP than with CPPV. ECWO is less effective in obese individuals than in those with normal body weight, and the effect of CPAP in overweight individuals is small.

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Although continuous positive pressure ventilation (CPPV) is widely used for patients requiring respiratory support, interest in negative pressure ventilation has returned in recent years,[1 2] partly because of a greater appreciation of the detrimental cardiovascular effects of CPPV. Compared with spontaneous ventilation, controlled positive pressure ventilation reduces cardiac output by reducing venous return.[3 4]

External chest wall oscillation (ECWO) by a Hayek oscillator is a recently developed mode that combines features of negative pressure ventilation and conventional high frequency oscillation.[5] A cuirass is used to oscillate the anterolateral area of the chest and upper abdomen with an average subatmospheric pressure. In contrast to previous attempts at ECWO that relied upon the elastic recoil of the chest wall, both the inspiratory and expiratory phases of ventilation are actively controlled.

By setting the end-expiratory chamber pressure at less than atmospheric, the decrease of functional residual capacity (FRC) could be reduced. However, in almost all studies carried out on anaesthetized humans, end-expiratory chamber pressure has been positive to achieve a sufficient pressure span for carbon dioxide removal.[6 7] In addition to this active compression of the chest, the required airtight seal of the cuirass itself may reduce FRC. These effects and the known decrease in FRC during anaesthesia may reduce the efficiency of ECWO by shifting the tidal range to the lower, flat portion of the volume-pressure curve of the respiratory system.

Continuous positive airway pressure (CPAP) is an established ventilatory adjunct that increases FRC.[8] Whether a certain value of CPAP improves alveolar gas exchange or over-distends the lung depends both on the initial level of the FRC and the compliance of the respiratory system. As reduction in FRC during anaesthesia is more marked in obese patients,[9] it can be assumed that the effects of CPAP differ between obese individuals and those with a normal body weight.

This study was designed to test the hypotheses that (1) the application of a CPAP improves pulmonary gas exchange during external chest wall oscillation, (2) the effects of CPAP depend upon body status, and (3) cardiac output is less impeded during ECWO plus CPAP than with CPPV.

Methods

The study protocol was approved by the ethical committee of Justus-Liebig-University Giessen, and written informed

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consent was obtained from each patient before the study began. The study consisted of two parts: in part one, the effects of a combination of four levels of CPAP with ECWO were investigated. Two groups of patients, with a body mass index of less and greater than 25, were compared. In part two, the haemodynamic effects of CPPV were compared with those of a combination of ECWO and CPAP. We chose the CPAP from the findings of part one of the study.

Twenty patients scheduled for elective lower abdominal surgery were enrolled into the first part of the study, meeting the following criteria: American Society of Anesthesiologists (ASA) physical status I and II, aged between 18 and 60 yr, body height between 170 and 190 cm, and male gender. Exclusion criteria were: a history of restrictive or obstructive pulmonary disorders, cardiovascular diseases, and a body mass index outside the range of 20–35.

Six patients classified as ASA physical status III and awaiting major abdominal surgery were included into the second part of the study. Patients were excluded if they had ventricular dysfunction classified as New York Heart Association (NYHA) function III or IV, unstable angina pectoris, or if pre-operative vital capacity (VC) or forced expiratory volume 1 s (FEV_1) were less than 90 or 80%, respectively, of the predicted norm.[10]

Pre-medication consisted of 7.5 mg orally administered midazolam given 45 min before the patients were transferred to the operating room. After pre-oxygenation, anaesthesia was induced with fentanyl 3–4 $\mu g\ kg^{-1}$ and propofol 2.0–2.5 mg kg^{-1}. Vecuronium 0.1–0.12 mg kg^{-1} was given to facilitate intubation. Trachea was intubated with a 10.0 mm ID tracheal tube (Mallinckrodt, Athlone, Ireland) via direct laryngoscopy. Anaesthesia and relaxation were maintained with a continuous infusion of propofol 100–120 $\mu g\ kg^{-1}\ min^{-1}$, fentanyl 2 $\mu g\ kg^{-1}\ h^{-1}$ and vecuronium 0.2 mg $kg^{-1}\ h^{-1}$.

Patients were in the supine position and connected to a Servo Ventilator 900C (Siemens-Elema AB, Solna, Sweden) and the lungs were ventilated in the volume-controlled mode. Initial ventilator settings were: a respiratory rate of 12 min^{-1}, an I:E ratio of 1:2 without an end-inspiratory pause, and a positive end-expiratory pressure of 5 cm H_2O. Tidal volume was initially set at 8–10 ml kg^{-1} and then adjusted to achieve normocapnia. An inspired oxygen fraction of 0.6 was used for both studies.

ECWO was delivered with a Hayek oscillator (Breasy Medical Equipment, London, UK). A cuirass of size 8 or 9 was placed over the anterior part of the chest and upper abdomen and sealed using Velcro straps placed around a bean filled pillow on which the patients were lying. The cuirass was connected via wide-bore tubing to a microprocessor-controlled power unit that contains a diaphragm pump. The initial oscillator settings were set as follows: frequency 60 min^{-1}, end-inspiratory chamber pressure –25 cm H_2O, end-expiratory chamber pressure 3 cm H_2O, I:E ratio 1:1. After 10 min, end-inspiratory and end-expiratory chamber pressure were adjusted to obtain a tidal volume of at least 170 ml and a mean chamber pressure between –5 and – 10 cm H_2O. The I:E ratio and frequency were kept constant during the study period.

CPAP was delivered with a high flow CPAP system (Continuous Flow CPAP-System FDF 2/G.C.V., B+P, Neunkirchen, Germany). Oxygen and nitrogen were set to a flow rate of 20 litre min^{-1}, resulting in a sum flow of 40 litre min^{-1}. CPAP level was adjusted by a spring-loaded valve (Ambu International A/S, Brondby, Denmark).

Standard monitors included a five-lead electrocardiograph (Sirecust 1280, Siemens Medical Electronics, Danvers, MA, USA) and a pulse oximeter (Nellcor Puritan Benett, Hayward, CA, USA). Each patient had a radial artery catheter (20 G, Vialon, Becton Dickinson, Heidelberg, Germany). A continuous intravascular blood gas system, consisting of fluorescent P_{O_2}, pH and P_{CO_2} sensors and a thermocouple (Paratrend 7+, Diametrics, High Wycombe, Bucks, UK) was inserted after *in vitro* calibration via the radial artery catheter. Continuous blood–gas monitoring was used to allow rapid adjustment of the ventilator settings and to assess blood gas stability before an *in vitro* analysis was performed. After each study period, arterial blood was sampled for *in vitro* blood gas measurement (NOVA Stat 5, Nova Biomedical, Waltham, MA, USA).

All patients of the second part of the study had a pulmonary artery catheter (Model 93A-434-7.5F G, Baxter Healthcare Corporation, Irvine, CA, USA) in place. Cardiac output was measured by the thermodilution technique, and the results of five measurements taken randomly through the respiratory cycle were averaged (Explorer RER, Baxter Healthcare Corporation, Irvine, CA, USA). Systemic and pulmonary artery pressure, pulmonary capillary wedge, and central venous pressure were recorded at end-expiration.

Flow and airway pressure were measured via a variable-orifice pneumotachograph with an integrated differential pressure transducer (VarFlex, Bicore Monitoring Systems, Irvine, CA, USA), positioned between the tracheal tube and the T-piece. Tidal volume (V_T), respiratory rate (RR) and expiratory minute ventilation (V_E) were obtained from the flow signal.

The first part of the study was conducted as a four-period crossover trial, with each combination of ECWO and CPAP studied for at least 15 min. Patients received in a randomized order ECWO with a CPAP of 0 (CPAP 0), 5 (CPAP 5), 10 (CPAP 10), and 15 (CPAP 15) cm H_2O. When blood gases remained stable for 10 min in the respective combination of ECWO and CPAP, *in vitro* blood gas analysis was performed and circulatory values were recorded.

In the second part of our investigation, ECWO plus CPAP and CPPV were randomly applied to each patient for 30 min. PEEP was set at 6 cm H_2O. Attention was paid to match CPAP and PEEP level. When blood gases and circulation were stable for at least 10 min, *in vitro* blood gases, circulatory and respiratory values were recorded.

Statistical analysis

Data were analysed using statistical software (SPSS release 9.01 for Windows; Chicago, IL, USA) running under Windows 98 (Microsoft Corporation, Redmond, WA, USA) on a personal computer. The two-sample *t*-test was used to compare biometric data between group 'O' with group 'N'. The general linear model (GLM) approach was used to perform repeated measures analysis of variance.[11] To assess the effect of CPAP on haemodynamics and gas exchange in part one of the study, a within-subject factor with four levels (CPAP 0, 5, 10, 15 cm H_2O) was defined. To compare CPPV with ECWO plus CPAP, a separate analysis with five levels (CPPV, CPAP 0, 5, 10, 15 cm H_2O) of the within-subject factor was performed. Differences between obese individuals and those with normal body weight were analysed by including a between-subject factor into the model. For any within-subjects effect, the Mauchly test of sphericity was performed. The Greenhouse–Geisser epsilon was used to correct the degrees of freedom if the assumption of sphericity was violated. When assessing the effects of CPAP, the four levels of the within-subjects factor were compared in each group by simple contrasts. Simple contrasts were also used to compare the effect of CPPV with those of ECWO plus CPAP. Bonferroni's correction was applied for double comparisons (contrasts in group 'O' and 'N').

In part two, comparisons between ECWO plus CPAP *vs* CPPV in ASA III patients were made by the Wilcoxon matched pairs test. All values are mean (SD), and statistical significance was inferred if $P<0.05$.

Table 1 Characteristics of patients in study one. BMI=body mass index; $^{\dagger}P<0.01$; $^{\ddagger}P<0.001$

	Group 'O' (*n*=10)	Group 'N' (*n*=9)
Age (yr)	52 (39–66)	46 (21–74)
Height (cm)	173 (11)	175 (7)
Weight (kg)	90 (15)†	71 (8)
BMI	29.9 (2.5)‡	23.7 (1.1)

Results

Among 20 patients who gave informed consent, one of group 'N' was excluded because of excessive pulmonary secretion during ECWO, which required repeated mechanical aspiration. The 19 remaining patients studied in part one of our investigation did not differ with respect to age and height. As required by the design, patients of the 'obese' group (group 'O') had a greater body mass index (Table 1).

CPPV vs ECWO+CPAP

Ventilator settings during ECWO and CPPV (Table 2) were comparable between the groups. During ECWO, measured CPAP levels were always higher than set at the PEEP valve.

Despite a decrease in tidal volume from 609 (125) to 193 (47) ml ($P<0.001$) after switching from CPPV to ECWO, blood gases remained constant in group 'N'.

With ECWO in group 'O', tidal volume decreased from 659 (98) to 175 (85) ml, $P<0.001$ and this was accompanied by decreases in Pa_{O_2} (24.3 (6.5) to 16.6 (4.4) kPa, $P<0.01$) and pH (7.43 (0.03) to 7.35 (0.05), $P<0.01$), whereas carbon dioxide tension increased from 4.7 (0.3) to 6.0 (0.8) kPa ($P<0.01$) (Table 3).

Response to CPAP during ECWO

Obese individuals and individuals with normal body weight responded differently when ECWO was combined with CPAP set at 5 cm H_2O. Whereas Pa_{CO_2} decreased in obese subjects (6.0 (0.8) to 5.6 (0.5) kPa, $P<0.05$), it increased in normal subjects with normal body weight (4.0 (0.6) to 4.5 (0.9) kPa, $P<0.05$). In group 'N', a further increase in CPAP to levels of 10 and 15 cm H_2O increased arterial P_{CO_2} to 4.9 (1.2) kPa ($P<0.05$) and 5.7 (1.7) kPa ($P<0.01$, Table 3), respectively.

Compared with CPAP 0, tidal volume decreased with CPAP 15 in group 'N' from 193 (47) to 150 (26) ml, $P<0.05$, and remained unchanged at all CPAP values in group 'O'.

Table 2 Ventilator settings during CPPV and ECWO. PIP, peak inspiratory pressure, PM, mean airway pressure, PEEP, positive end-expiratory pressure, Pinsp, peak inspiratory chamber pressure; Pexp, end-expiratory chamber pressure; MCP, mean chamber pressure; ΔPressure, chamber pressure span

		Group 'O' (*n*=10)	Group 'N' (*n*=9)	Statistical significance
CPPV	PIP (cm H_2O)	20 (4)	18 (4)	n.s.
	PM (cm H_2O)	10 (1)	9 (3)	n.s.
	PEEP (cm H_2O)	7 (1)	6 (1)	n.s.
ECWO	Frequency (min^{-1})	60 (0)	60 (0)	n.s
	I:E ratio	1:1	1:1	n.s
	Pinsp (cm H_2O)	–22.9 (4.8)	–20.2 (3.9)	n.s.
	Pexp (cm H_2O)	+5.9 (2.0)	+3.4 (3.5)	n.s
	MCP (cm H_2O)	–6.3 (1.5)	–6.7 (2.4)	n.s.
	ΔPressure (cm H_2O)	28.8 (6.2)	23.6 (6.0)	n.s.

Table 3 Respiratory mechanics, arterial blood gases and haemodynamics during ECWO plus CPAP (group 'N'· n=9, group 'O' n=10). PIP, peak inspiratory pressure, PM, mean airway pressure; CPAP, continuous positive airway pressure, VTe, expiratory tidal volume; AaGrad, alveolar-arterial oxygen gradient. *Difference between group 'O' and 'N' at P<0.05, †Difference between group 'O' and 'N' at P<0.01; ‡Difference between group 'O' and 'N' at P<0 001; §Difference from 'ECWO+CPAP 0' at P<0 05

	Group	ECWO+CPAP 0	ECWO+CPAP 5	ECWO+CPAP 10	ECWO+CPAP 15
PIP (cm H_2O)	N	5 (0)	12 (1)	16 (1)	21 (2)
	O	5 (1)	11 (1)	16 (2)	21 (3)
PM (cm H_2O)	N	3 (1)	9 (1)	13 (1)	19 (1)
	O	3 (1)	9 (1)	13 (2)	18 (2)
CPAP (cm H_2O)	N	3 (0)	9 (1)	12 (1)	19 (1)
	O	3 (1)	9 (1)	11 (1)	19 (2)
*V*Te (ml)	N	193 (47)	170 (30)	160 (26)	150 (26)§
	O	175 (85)	179 (57)	174 (57)	163 (51)
PH	N	7 46 (0 07)	7.43 (0.07)	7 40 (0.08)§	7.36 (0.11)§
	O	7.35 (0 05)*	7.36 (0.04)§	7 34 (0.06)	7 31 (0 08)
Pa_{CO_2} (kPa)	N	4.0 (0.6)	4 5 (0 9)§	4.9 (1.2)§	5.7 (1 7)§
	O	6.0 (0.8)†	5 6 (0 5)§	6.1 (1.0)	6.6 (1.2)
Pa_{O_2} (kPa)	N	31.7 (9.0)	33 6 (7 2)	34.0 (6.7)	34.4 (7.3)
	O	16.6 (4 4)‡	18.2 (4 7)	18.3 (4 9)	20.2 (5 2)
$PA_{O_2} - Pa_{O_2}$	N	24.9 (2.3)	23.0 (2 0)	22.5 (1.9)	22.0 (2 1)
	O	39.9 (2.2)‡	38.3 (1.9)	38 1 (1.8)	36.2 (2.0)
HR (beats min^{-1})	N	54 (11)	56 (11)	55 (11)	59 (10)
	O	59 (10)	59 (10)	58 (10)	59 (12)
MAP (mm Hg)	N	83 (19)	84 (18)	82 (19)	81 (19)
	O	79 (11)	79 (12)	80 (12)	78 (12)

Table 4 Ventilator settings in six ASA III patients

	CPPV	ECWO+CPAP	Statistical significance
PIP (cm H_2O)	19 (1)	11 (2)	<0 05
PM (cm H_2O)	10 (1)	8 (1)	<0.05
PEEP (cm H_2O)	6 (1)	7 (1)	n s
V_Te (ml)	685 (72)	193 (27)	<0 05
RR (min^{-1})	12 (1)	60 (0)	–
I:E	1:2	1:1	–
Pinsp cuirass (cm H_2O)	–	–24 6 (6 8)	–
Pexp cuirass (cm H_2O)	–	4.0 (3.1)	–
ΔP cuirass (cm H_2O)	–	28 6 (4 1)	–
MCP (cm H_2O)	–	–8.3 (4 7)	–

Table 5 Cardiovascular measurements and blood gases in six ASA III patients, *P<0.05

	CPPV	ECWO+CPAP
CI (litre min^{-1} m^{-1})	2.1 (0.2)	2.7 (0.5)*
HR (beats min^{-1})	66 (10)	65 (9)
MAP (mm Hg)	77 (15)	79 (5)
MPAP (mm Hg)	17 (6)	20 (6)
PCWP (mm Hg)	10 (4)	9 (4)
CVP (mm Hg)	7 (5)	7 (4)
SVI (ml m^{-2})	32 (6)	49 (9)*
SVRI (dyn s cm^{-5} m^2)	2659 (808)	2215 (892)
PVRI (dyn s cm^{-5} m^2)	275 (85)	330 (62)*
PH	7.45 (0.05)	7.22 (0.39)*
Pa_{CO_2} (kPa)	4.6 (0.4)	5.3 (1.0)
Pa_{O_2} (kPa)	25.9 (7.2)	22.1 (7.7)
Sa_{O_2} (%)	100 (1)	99 (1)
Sv_{O_2} (%)	73 (5)	77 (4)*
Do_2 (ml min^{-1} m^{-2})	309 (29)	383 (64)*
Vo_2 (ml min^{-1} m^{-2})	90 (15)	88 (19)
Qs/Qt (%)	13 (2)	19 (2)
Oxygen extraction (%)	29 (5)	23 (2)

Differences between the groups

Arterial Po_2 (P<0.001) and pH (P<0.05) were greater, and Pa_{CO_2} (P<0.01) was less in subjects with normal body weight, irrespective of the ventilation used. In obese patients, the alveolar-arterial oxygen difference was greater during CPPV and ECWO plus CPAP (P<0.01).

Haemodynamics in ASA III patients

In part two of our investigation, seven patients agreed to participate, but one patient was excluded because of supraventricular arrhythmia immediately before the study began. Therefore, six patients (aged 60 (12) yr (range 41–75), height 178 (6) cm, weight 96 (13) kg, body mass index 30.5 (3.7), ASA physical status III (0)) were studied.

Respiratory mechanics for CPPV and ECWO+CPAP are given in Table 4.

PEEP and CPAP, respectively, were similar during both ventilatory modes. Peak inspiratory pressure (19 (1) *vs* 11 (2) cm H_2O, P<0.05), mean airway pressure (10 (1) *vs* 8 (1) cm H_2O, P<0.05) and tidal volume (685 (72) *vs* 193 (27) ml, P<0.05) were inherently greater during CPPV.

The results of invasive circulatory and blood gas measurements are shown in Table 5. Cardiac index (2.7 (0.5) *vs* 2.1 (0.2) litre min^{-1} m^{-2}, P<0.05), stroke volume (SVI 49 (9) *vs* 32 (6) ml m^{-2}, P<0.05) and oxygen delivery (383 (84) *vs* 309 (29) ml min^{-1} m^{-2}, P<0.05) were greater during ECWO+CPAP. A tendency for greater Pa_{O_2} and less Pa_{CO_2} during CPPV was statistically not significant.

Discussion

In this study population of anaesthetized and paralysed patients, we have shown that (1) during ECWO, the effects of CPAP on pulmonary gas exchange are different in obese individuals and in those with normal body weight, and (2) that a combination of ECWO and CPAP allows a greater cardiac output than conventional positive pressure ventilation.

In 10 subjects with normal body build, arterial $P\text{CO}_2$ and $P\text{O}_2$ did not differ between CPPV and ECWO. When ECWO was combined with CPAP, each increase in CPAP was accompanied by a decline in tidal volume and an increase in Pa_{CO_2}. As the alveolar-arterial difference for oxygen remained constant, the increases in Pa_{CO_2} with increasing CPAP can be attributed to alveolar hypoventilation.

Our obese individuals had a different response to CPAP during ECWO. We proposed that increasing the FRC with CPAP would improve carbon dioxide elimination by recruiting unventilated alveoli and by reducing the over-expansion of the remaining lung,[12] but the effect of CPAP 9 (2) cm H_2O on Pa_{CO_2} was small. Because the chosen CPAP between 3 and 19 cm H_2O should offset the FRC reduction in obese, but otherwise healthy subjects, we assume that the limited effect of CPAP on gas exchange was because of its distribution within the thorax. In the supine position, CPAP preferentially distends upper lung zones,[13 14] whereas the changes in FRC predominantly affect dependent lung zones.[15] The negative pressure from the cuirass was applied to the anterior part of the chest, which could have augmented the preferred distension of upper lung zones by CPAP.

Compared with the subjects of normal body weight, arterial oxygenation in the obese individuals was already less during CPPV, and their oxygenation decreased when ECWO was started. Ventilation-perfusion inequality may contribute to their impaired oxygenation. Overweight patients develop more extensive compression atelectasis during anaesthesia.[16] Whether compression by the cuirass affects the development of atelectasis and is more marked in obese individuals, remains unclear.

Despite greater use of ECWO, for instance in microlaryngeal surgery,[17] some problems regarding its efficiency in anaesthetized patients remain to be resolved.

Normal subjects, awake or anaesthetized, can be ventilated efficiently with ECWO alone. To evaluate a prototype chest wall oscillator, Dolmage and co-workers[18] studied seven volunteers with a body mass index of 24.3 (1.8). With a chamber pressure span of 25.1 (3.3) cm H_2O, which was comparable to ours, their subjects ceased spontaneous breathing at oscillatory frequencies of 60–90 min^{-1}. Five minutes of ECWO at a frequency of 60 min^{-1} and a tidal volume of 344 (34) ml decreased Pa_{CO_2} by 13 (1) mm Hg. In our study, ECWO with comparable oscillator setting was as effective as CPPV, although our subjects had been anaesthetized and ventilated in the supine position.

In contrast to normal body subjects, our obese subjects were substantially less effective ventilated by ECWO. Despite careful setting of the airtight seal of the cuirass, we repeatedly failed to achieve normocapnia by increasing chamber pressure span. Problems in achieving effective ventilation by ECWO alone have been reported by Shekerdemian and colleagues.[19] In their study, pressure support was applied to overcome tube resistance. Pressure support ventilation (PSV) was also combined with ECWO by Takeda and co-workers,[7] although their patients were breathing spontaneously. Whether PSV or other ventilatory adjuncts in combination with ECWO are more effective in overweight patients or those with pulmonary disease, awaits further study.

In our study, tidal volumes in the range of 150–200 ml raise the questions about the underlying mechanisms of gas exchange. Venegas and colleagues developed a mathematical model which describes the general relationship between gas transport, tidal volume, and respiratory rate. The transition from conventional ventilation to high-frequency ventilation occurred when the alveolar ventilation per breath was 20% of the volume of the conducting airways (V_D), and the tidal volume is 1.2 times V_D.[20] The tidal volumes in our investigation were almost always more than 1.2 times the calculated V_D and the calculated alveolar ventilation per breath exceeded 20% of V_D, so gas exchange in our subjects was predominantly governed by conventional gas transport.

In our six ASA III patients, cardiac output and stroke volume were greater with ECWO plus CPAP than with CPPV. The effects of positive pressure ventilation on cardiovascular function have been studied repeatedly.[21] In brief, increasing intrathoracic pressure by CPPV decreases both venous return to the right ventricle (RV) and augments left ventricular (LV) ejection by decreasing LV afterload. Variations in right atrial pressure are the primary factor determining the fluctuation in pressure gradient for systemic venous return during ventilation. Increases in intrathoracic pressure (ITP) by CPPV decrease venous blood flow by increasing right atrial pressure.[22] The decrease in venous return is partially offset by an accompanying increase in abdominal pressure tending to maintain mean systemic pressure relative to right atrial pressure constant.[23] Left ventricular afterload is determined by systolic wall tension which is proportional to the product of transmural LV pressure and the radius of curvature of the LV. Provided that LV inside pressure during ejection remains unaltered, increases in intrathoracic pressure by CPPV should decrease LV afterload by reducing its transmural pressure gradient. Besides the effects on transmural LV pressure, CPPV also decreases LV afterload by impeding venous return, thus decreasing the end-systolic LV radius of curvature.

The net effect of an impeded venous return and the decrease in LV afterload on cardiac output is determined by the volume status and the cardiac function. When LV function is impaired, cardiac output increases in response to rises in ITP as the decrease in LV afterload has a greater effect than the decrease in LV filling pressure.[24] When LV function is normal, increase in ITP will reduce cardiac output as the decrease in venous return has more effect than the increase in LV afterload.[25]

In our study of patients without severe left ventricular dysfunction, cardiac output was greater during ECWO plus CPAP than with CPPV. Based on the assumption of a smaller ITP during ECWO, the increase in cardiac output can be explained by an improvement in venous return that offset the increase in LV afterload. This corresponds with the findings of an experimental study by Lockhat and co-workers, who found that devices, which confine negative pressure to the thorax and upper abdomen, increase cardiac output by raising the gradient for venous return.[26]

The value of ECWO in cardiac failure remains to be clarified. The haemodynamic effects of ECWO and CPPV are similar when cardiac failure has been induced by a β-blocking agent.[27] Cardiac function improves with external high-frequency oscillation in patients with NYHA physical status I and II after coronary artery bypass grafting.[6] In patients with cardiac arrest coronary perfusion pressure was augmented by ECWO when compared with standard cardiopulmonary resuscitation. The increase in coronary perfusion pressure was attributed to an increased gradient between the aortic and the atrial pressure.[28]

In conclusion, ECWO during anaesthesia and muscle relaxation is less effective in obese individuals than in normal subjects. CPAP only slightly improves pulmonary gas exchange in overweight individuals. Because of the favourable haemodynamic effects of ECWO, a systematic investigation of methods to increase the efficiency of this technique may be useful.

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Perianaesthetic risks and outcomes of abdominal surgery for metastatic carcinoid tumours[†]

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Patients with metastatic carcinoid tumours often undergo surgical procedures to reduce the tumour burden and associated debilitating symptoms. These procedures and anaesthesia can precipitate a life-threatening carcinoid crisis. To assess perioperative outcomes, we studied retrospectively the medical records of adult patients from 1983 to 1996 who underwent abdominal surgery for metastatic carcinoid tumours. Preoperative risk factors, intraoperative complications and complications occurring in the 30 days after surgery were recorded. Perioperative complications or death occurred in 15 of 119 patients (12.6%, exact confidence interval 7.2–19.9). None of the 45 patients who received octreotide intraoperatively experienced intraoperative complications compared with eight of the 73 patients (11.0%) who did not receive octreotide (P=0.023). The presence of carcinoid heart disease and high urinary output of 5-hydroxyindoleacetic acid preoperatively were statistically significant risk factors for perioperative complications.

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The perioperative course and anaesthetic management of patients with carcinoid tumours have been described only anecdotally because of the low incidence of symptomatic tumours that require surgical intervention.[1–23] Given an annual incidence of 0.28 per 100 000 population, the average general surgeon in the USA will see approximately one case every 50 yr.[23] Most, but not all, carcinoid tumours that are surgically managed are metastatic from a gastrointestinal origin. Patients with these metastatic carcinoid tumours often undergo surgical procedures to reduce the tumour burden and associated debilitating symptoms despite the fact that these procedures and anaesthesia can precipitate a life-threatening carcinoid crisis.[1–3] Unfortunately, the frequencies, outcomes and factors predictive of complications in this population of surgical patients are unknown. To address this problem, we evaluated the perioperative courses and anaesthetic management of 119 adult patients who underwent elective surgery for symptomatic carcinoid tumours at a single institution and by one surgeon during a 14 yr period.

Methods

With approval of the Mayo Institutional Review Board, we identified consecutive adult (18 yr of age or older) patients from 1 January 1983 to 31 December 1996, who underwent abdominal surgery for metastatic carcinoid tumours by one surgeon at our institution. For patients who had multiple abdominal operations for symptomatic carcinoid, only the first operation was included. Abdominal procedures included hepatic arterial ligation, resection or biopsy of hepatic metastases, hepatic carcinoid cryotherapy, and small or large bowel resection or diversion. One or more of these procedures could have been performed during the first operation.

The perioperative medical, surgical, nursing and anaesthesia records of 119 patients were reviewed to identify preoperative risk factors, intraoperative complications and

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postoperative complications occurring up to 30 days after surgery according to well-established criteria.[24 25]

Preoperative information included age, sex, the presence of comorbid disease [cardiovascular, renal, biliary, central nervous system (CNS), respiratory], the presence of carcinoid heart disease as determined by a cardiologist and confirmed by a preoperative echocardiogram, American Society of Anesthesiology physical status, preoperative symptoms of flushing, diarrhoea and/or shortness of breath, preoperative use of bronchodilators, corticosteroids and histamine receptor type 2 antagonists, the preoperative daily dose of octreotide, the dose of octreotide administered in the 8 h preceding the start of anaesthesia, the site of the primary carcinoid tumour, if known, and the most recent preoperative urinary output of 5-hydroxyindoleacetic acid (5-HIAA).

Intraoperative information included the type and duration of anaesthesia, the principal maintenance anaesthetic agent, the use of invasive monitors, the volume and type of i.v. fluids and blood products administered, and the total amount of octreotide administered during anaesthesia. Intraoperative observations included the presence of flushing, urticaria, ventricular dysrhythmia, bronchospasm, acidosis (defined as arterial pH <7.2), lowest Pa_{O_2}, lowest Sp_{O_2}, lowest systolic blood pressure (SBP), highest SBP, death, total duration of SBP <80 mm Hg to the nearest 5 min, and treatment with vasopressor(s) (SBP <80 mm Hg for >10 min), and total duration of sustained tachycardia (defined as pulse >120 beats min^{-1}) to the nearest 5 min.

Postoperative morbidity occurring within 30 days of the index surgery was identified using criteria developed by Hosking *et al.*[25] and detailed elsewhere.[26] Adverse outcomes included myocardial infarction, pulmonary embolism, CNS changes, renal dysfunction, biliary dysfunction, prolonged endotracheal intubation, systemic sepsis and death.

Statistical analysis

Univariate analyses of potential risk factors were performed using the rank sum test for continuous variables and Fisher's exact test for categorical variables. Exact confidence intervals for complication frequencies were calculated. In all cases, two-sided tests were performed and $P \leq 0.05$ was used to denote statistical significance.

Results

One hundred and nineteen patients underwent abdominal surgery by one surgeon for metastatic carcinoid tumours during the study period. The median age at the time of surgery was 59 yr (range 30–78 yr). The percentages of male and female patients were similar (53.8 and 46.2% respectively). Before surgical intervention, 76 patients (64%) had experienced flushing, 83 patients (70%) had intermittent or sustained diarrhoea and 15 patients (12.6%) had episodes of shortness of breath. The median preoperative urinary 5-HIAA output was 96 mg/24 h (502.1 μmol day^{-1}) (range 3.9–837 mg/24 h) (20.4–4377.5 μmol day^{-1}). Twenty-four patients (20%) had carcinoid heart disease. Thirty-one patients (26%) received octreotide preoperatively, with a median dose of 300 μg intravenously or subcutaneously (range 50–1000 μg). Only six of these patients did not receive any additional octreotide intraoperatively. Forty-five patients (38%) received octreotide intraoperatively, with a median dose of 350 μg i.v. or s.c. (range 30–4000 μg) (Table 1). All patients received narcotics and volatile anaesthetics intraoperatively. Vasopressors were used in 43% of patients, phenylephrine was used in 31% and ephedrine in 16%.

Table 1 Procedural characteristics for 118 patients who underwent abdominal resection of carcinoid tumours during 1983–1996 All intraoperative data were missing from one patient's medical record

Characteristic	Value
Surgery type (%)	
Resection of carcinoid tumour	48.3
Arterial ligation	19.5
Other intra-abdominal procedure	32.2
Primary induction agent (%)	
Thiopental sodium	71.2
Etomidate	22.9
Propofol	4.2
Other	1.7
Volatile anaesthetic use (%)	100.0
Narcotic	100.0
Succinylcholine	63.6
Primary neuromuscular blocking agent (%)	
Vecuronium	78.0
Pancuronium	11.9
Atracurium	7.6
Other	1.7
Intraoperative vasopressor use (%)	42.9
Phenylephrine	31.4
Ephedrine	16.1
Dopamine	1.7
Epinephrine	0.8
Mephentermine	0.8
Artery catheter (%)	90.7
Central venous catheter (%)	61.0
Pulmonary arterial catheter (%)	3.4
Intraoperative octreotide (μg)	39.8
Mean (SD) (μg)	523.0 (624.8)
Median (μg)	350
Range (μg)	30–4000
Duration of anaesthesia (min)	
Mean (SD)	244.7 (76.9)
Median	240
Range	105–455

Perioperative complications or death occurred in 15 of 119 patients [12%, 95% confidence interval (CI) 7.2–19.9%]. Patients who experienced perioperative complications had a higher frequency of carcinoid heart disease than those who did not experience complications (53 *vs* 15%, $P=0.002$). Although most patients (94%) had a preoperative urinary 5-HIAA output that was above normal (>6.0 mg/24 h) (>31.4 μmol day^{-1}), the median urinary 5-HIAA output was significantly higher in patients who

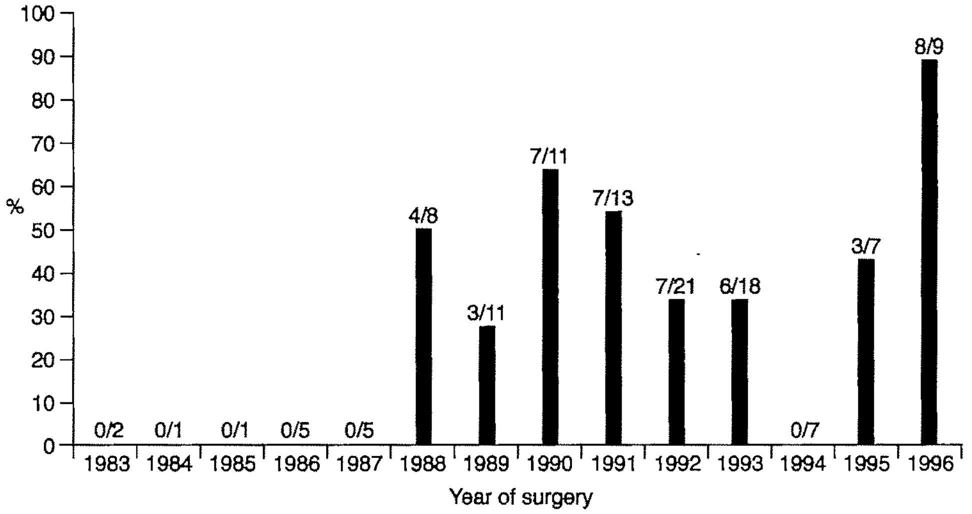

Fig 1 Percentage of patients receiving octreotide intraoperatively. Octreotide was available on a compassionate-use basis from 1984 to 1987 and received FDA approval in 1988. Its intraoperative use began in 1988 for the patients in our study.

experienced complications (200 *vs* 78 mg/24 h, $P<0.006$) (1046 *vs* 407.9 µmol day^{-1}).

Of the 15 patients who experienced perioperative complications or death, eight experienced one or more intraoperative complications. Intraoperative complications included flushing in four patients, sustained hypotension in two patients, and bronchospasm, acidosis and ventricular tachycardia in one patient each. There were no intraoperative deaths, episodes of urticaria or ventricular fibrillation.

None of the 45 patients who received octreotide intraoperatively experienced significant intraoperative complications compared with eight of the 73 patients (11%) who did not receive octreotide ($P=0.023$). Patients who received octreotide intraoperatively and those who did not had similar preoperative characteristics, similar comorbidities including carcinoid heart disease and similar preoperative urinary 5-HIAA output. Octreotide received approval by the Food and Drug Administration (FDA) in 1988, and intraoperative use in this study began in the same year (Fig. 1). We performed an additional analysis restricted to the period during which octreotide was approved for use by the FDA (1988–1996) to rule out any confounding variables created by possible changes in anaesthetic or surgical management after 1988. This analysis demonstrated that patients receiving octreotide intraoperatively experienced significantly fewer intraoperative complications than patients who did not receive octreotide (0/45 *vs* 8/60, $P=0.010$)

Of the six patients who received octreotide only preoperatively, one (17%) developed an intraoperative complication. Four of the 45 patients (9%) who received octreotide intraoperatively developed postoperative complications. We therefore have no evidence that preoperative administration of octreotide is associated with a reduced frequency of intraoperative complications or that intraoperative administration is associated with a reduced frequency of postoperative complications.

Nine patients experienced one or more postoperative complications. Four patients (3%) developed biliary dysfunction, two patients had renal dysfunction and one patient required prolonged endotracheal intubation. Three patients (2.5%) died postoperatively. Details of the events preceding the three deaths follow.

Death 1

A 67-yr-old woman with severe carcinoid heart disease and a preoperative 5-HIAA output of 218 mg/24 h (1140.1 µmol/24 h) underwent a right hemicolectomy, ileotransverse colostomy, wedge biopsy of the right lobe of the liver and cholecystectomy for carcinoid of the small bowel, hepatic metastasis and cholelithiasis. Surgery was uneventful, and she was haemodynamically stable throughout the procedure. Twelve days later, the ileotransverse colostomy partially dehisced and she underwent resection of a portion of the terminal ileum and proximal transverse colon and an end-to-end ileotransverse colostomy. Four days after surgery, she developed intra-abdominal sepsis. She died 2 days later.

Death 2

A 30-yr-old man with Wolff–Parkinson–White ventricular pre-excitation syndrome, severe carcinoid heart disease and a preoperative urinary 5-HIAA output of 495 mg/24 h (2588.9 µmol day^{-1}) underwent hepatic artery ligation, resection of a portion of the ileum, and an end-to-end ileo-ileostomy for metastatic carcinoid tumour of the ileum. He was haemodynamically stable throughout the procedure. Postoperatively, he experienced progressive fluid retention (7.5 kg in 9 days) that was refractory to diuresis, as well as dyspnoea and bronchospasm, abdominal distension and lower extremity oedema. Ten days after surgery, he developed shortness of breath, sinus tachycardia and hypotension. These symptoms and signs deteriorated rapidly into electromechanical dissociation from which he could not be resuscitated.

Death 3

A 50-yr-old man was admitted to another hospital for nausea and vomiting, and was found to have abnormal liver function tests. He was transferred to our hospital 8 days later for further evaluation. Computed tomography of the abdomen revealed hepatic lesions consistent with metastases. Preoperative laboratory investigations included a preoperative urinary 5-HIAA output of 837 mg/24 h (4377.5 μmol day^{-1}), an aspartate aminotransferase concentration of 89 U $litre^{-1}$, alkaline phosphatase of 590 U $litre^{-1}$, total bilirubin of 5.0 mg dl^{-1} (85.5 μmol $litre^{-1}$) and direct bilirubin of 3.4 mg dl^{-1} (58.1 μmol $litre^{-1}$). A transthoracic echocardiogram demonstrated moderate tricuspid valve regurgitation, but the valves were insufficiently visualized to make a definitive diagnosis of carcinoid heart disease. Five days after admission the patient underwent a retrocolic, isoperistaltic gastrojejunostomy for gastric outlet obstruction secondary to metastatic carcinoid tumour. At surgery, his liver was noted to be 50–75% replaced by tumour. Surgery and anaesthesia were uneventful, and he was haemodynamically stable throughout the procedure. He was discharged 8 days after surgery and died 1 week later of unknown cause(s). No autopsy was performed.

Discussion

The major finding of this study is that the use of octreotide intraoperatively for patients with metastatic carcinoid tumours undergoing intra-abdominal surgery was associated with a decreased frequency of intraoperative complications. Also, the presence of carcinoid heart disease and high preoperative urinary 5-HIAA output were statistically significant risk factors for perioperative complications including death.

There are several case series of patients with metastatic carcinoid tumours. Two of these case series predate the availability of octreotide. Kleine *et al.*[20] described the anaesthetic management and intraoperative course of three surgical patients. All three of these patients experienced intraoperative hypertension, one patient also experienced an episode of hypotension and flushing and there were no intraoperative deaths. Miller *et al.*[19] reviewed the intraoperative management of nine patients. Again, no intraoperative deaths were noted. However, one patient had life-threatening haemodynamic instability, four other patients had hypertensive episodes and another developed bronchospasm.

Two more recent case series include reports of patients who received octreotide perioperatively. Ockert and White[4] reviewed the perioperative outcomes of six patients who underwent cardiac surgery for carcinoid heart disease. Four patients received octreotide perioperatively. One patient with widespread carcinoid metastases and carcinoid heart disease received octreotide pre- and intraoperatively but still experienced an intraoperative carcinoid crisis. This patient developed a severe coagulopathy after cardiopulmonary bypass and died within 12 h of surgery. The other three patients who received perioperative octreotide did not experience a carcinoid crisis intraoperatively, but one never recovered after the operation and died of respiratory failure and multiple metastases several months later. Veall *et al.*[22] reviewed 22 anaesthetic records of 21 patients with carcinoid syndrome who underwent laparotomy. Eight patients received octreotide preoperatively, and further boluses were administered intraoperatively to an unspecified number of patients. There were no intraoperative deaths, but two patients had sustained tachycardia and another two patients exhibited flushing intraoperatively. It is not stated whether these patients received octreotide intraoperatively. After the introduction of octreotide, intraoperative hypotension was generally reported to be less severe and was rapidly responsive to additional i.v. boluses of octreotide.

Urinary 5-HIAA appears to be a good biological marker for the assessment of carcinoid tumour activity[23] and its association with perioperative morbidity. We found that patients who had higher preoperative urinary 5-HIAA output were more likely to develop perioperative complications, including death. Similarly, Connolly *et al.*[27] reviewed the perioperative courses of 26 patients who underwent cardiac surgery for carcinoid heart disease and found that high preoperative urinary 5-HIAA output predicted decreased survival after operation. Their finding is not surprising because involvement of the heart disease is typically a late manifestation in the course of carcinoid disease. Pellika *et al.*[28] found that the mean output of urinary 5-HIAA among patients with carcinoid tumours was higher in 74 patients with carcinoid heart disease than in 51 patients without carcinoid heart disease (270 *vs* 131 mg/24 h, $P<0.001$) (1412.1 *vs* 685.1 μmol day^{-1}). However, an association between high preoperative urinary 5-HIAA output and perioperative morbidity was not detected in the series of 21 patients reviewed by Veall *et al.*[22] These authors noted that preoperative urinary 5-HIAA output was a poor predictor of perioperative cardiovascular stability in their patient population. In fact, severe hypotension occurred in one patient with a preoperative urinary 5-HIAA output of 11.8 mg/24 h (62 μmol day^{-1}).

Two of the three postoperative deaths in our study occurred in patients with severe carcinoid heart disease. The other death occurred in a patient with tricuspid regurgitation, whose valves were poorly visualized on transthoracic echocardiogram and therefore a definitive diagnosis of carcinoid heart disease could not be made. Patients with carcinoid heart disease usually experience symptoms of carcinoid syndrome (i.e. flushing, diarrhoea and shortness of breath) along with the symptoms of right-sided heart failure because of carcinoid-induced tricuspid or pulmonary valve involvement. Carcinoid heart disease and the associated right heart failure are a major cause of morbidity and mortality in these patients.[27]

Limitations of our study include the reliability of data notation on the medical record. However, we used rigorous definitions and abstracted only major events to increase our chances of capturing information reliably. There is clearly a referral bias at this tertiary care centre in that the patients in this study are not representative of any general population. It is quite likely that referred patients have more severe carcinoid disease, more comorbidities, and require more extensive surgery than those from our local population. We did not assess geographical characteristics in this study. The retrospective nature of this study precludes discovery of the reasons for which octreotide was administered before or after operation. It also prevents us from evaluating any causal relationship between medications or risk factors and perioperative complications. Specifically, this study was not able to evaluate the efficacy of intraoperative octreotide therapy to prevent intraoperative carcinoid crises. Additionally, although this investigation identified some characteristics that were associated with perioperative complications, the interpretation of no association between other patient or procedural characteristics and perioperative complications should be made with caution. In general, with only 15 of 119 patients experiencing complications, an analysis of potential risk factors has statistical power of less than 55% to detect a risk factor with a corresponding odds ratio of 3.0.

Our findings suggest that most people with metastatic carcinoid tumours can undergo intra-abdominal surgery safely. In our patient population, no intraoperative complications occurred in those who received octreotide intraoperatively. Overall, perioperative complications and death were strongly associated with the preoperative presence of carcinoid heart disease and higher elevated urinary 5-HIAA output.

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Use of angulated video-intubation laryngoscope in children undergoing manual in-line neck stabilization

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Laryngeal views obtained during direct laryngoscopy with and without manual in-line neck stabilization (MILNS) and during video-assisted intubation with MILNS using the angulated video-intubation laryngoscope were assessed in 100 paediatric patients (aged 0.25–17.3 yr). Visualization of the larynx (Cormack and Lehane score) as well as time taken for video-assisted tracheal intubation by six nurses and four resident anaesthetists not experienced in the technique were recorded. Cormack and Lehane scores were significantly worse during direct laryngoscopy when MILNS was applied. Video-assisted visualization of the larynx during MILNS produced scores, which were as good or better than those observed during direct laryngoscopy alone. Intubation times ranged from 19–75 s (mean 35 (SD 13.4); median 32).

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In children suffering from congenital syndromes associated with cervical spine instability, flexible fibre-optic-tracheal intubation, or proper care during direct laryngoscopy is mandatory to reduce the risk of neurological damage.[1–6] Direct laryngoscopy with minimal force and manual in-line neck stabilization (MILNS) is a commonly used technique for tracheal intubation in under these circumstances.[7] However, MILNS impedes direct laryngeal visualization, increasing the probability that external laryngeal manipulation and/or blind tracheal intubation may be required.[8–10]

The angulated video-intubation laryngoscope (AVIL) is a new endoscopic intubation device designed to improve glottic visualization when direct laryngoscopy is difficult or impossible (Fig. 1).[11] It consists of a cast plastic intubation laryngoscope with a blade angulated distally, similar to the activated McCoy laryngoscope.[12] The vertical flange of the blade is flattened, which improves sagittal manoeuvring and allows its use in paediatric patients. A thin channel leads from the handle to the tip of the blade and permits insertion of a fibre-optic endoscope (external diameter: 2.8 mm; length 1.8 m; manufacturer: Volpi AG, Schlieren, Switzerland). The endoscope carries optic fibres for image transmission (10 000 pixels) and light fibres for airway illumination. The viewfinder of the endoscope is attached to a conventional video-endoscope camera system and the light-adaptor is connected to a standard light source by means of a light cable. Because of the angulated tip, the device provides an improved view of the vocal cords, which is transmitted to a bedside video monitor.

The aim of this study was to assess the ability of inexperienced operators to obtain a good view of the larynx using the AVIL in the presence of MILNS in infants and children during tracheal intubation.

Methods

With approval of the hospital's Institutional Review Board, we enrolled 100 consecutive patients, who satisfied the following inclusion criteria: ASA I or II, age from birth to 18 yr, scheduled for elective surgery requiring orotracheal intubation, and no indication for rapid sequence induction. Pre-medication and induction of anaesthesia (inhalational or i.v.) depended upon the patient's medical condition and preference. Routine monitoring included praecordial stetho-

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[†] Declaration of interest: Dr Weiss is the inventor of the angulated video-intubation laryngoscope, which has been realised with a local fibre-optic manufacturer (Volpi AG, Schlieren, Switzerland). The manufacturer has provided the equipment for the study without charge. Dr Weiss does not hold any patent rights or agreements on the device nor does he receive any financial support from the manufacturer for the study.

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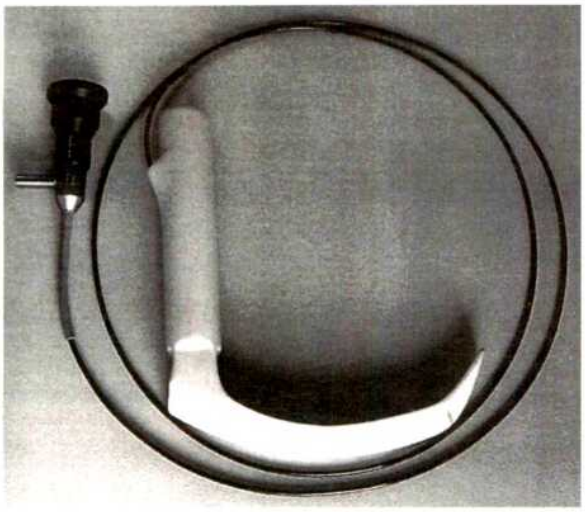

Fig 1 Angulated video-intubating laryngoscope consisting of a plastic cast, compact laryngoscope with an integrated ultrathin fibre-optic endoscope. The proximal ocular and light adaptor is connected to a bedside video-endoscopy system.

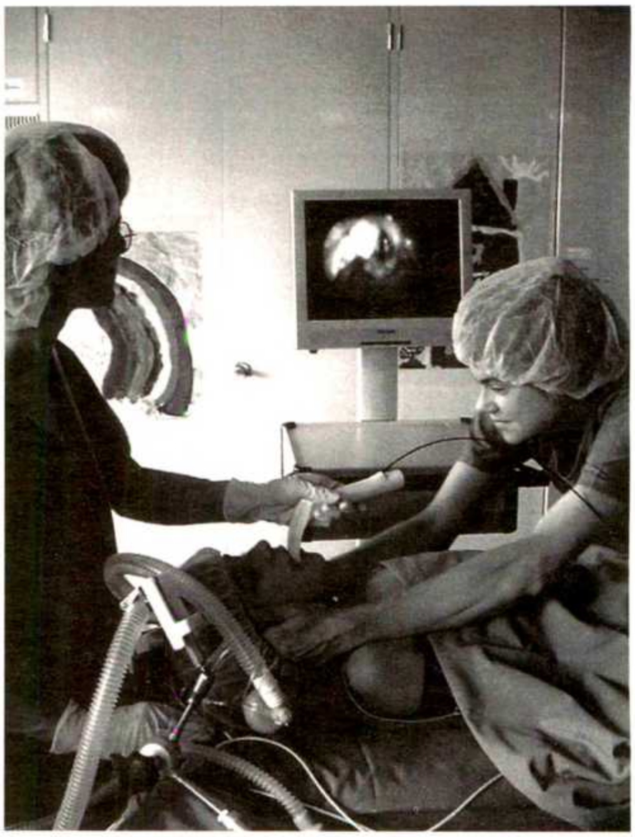

Fig 2 Video-assisted tracheal intubation in the presence of MILNS in an 11-yr-old child using the angulated video-intubation laryngoscope. The monitor gives a display of the vocal cords from the angulated blade tip for endoscopic guidance of the tracheal tube (with permission of a patient).

scope, pulse oximetry, electrocardiography and non-invasive blood pressure recording. After adequate mask ventilation was achieved, a non-depolarizing neuromuscular blocking agent was administered and anaesthesia was maintained with sevoflurane in oxygen. Before starting intubation, the AVIL (Fig. 1) was connected to a video-endoscopy system. An anti-fog agent was applied to the lens tip and the device was checked for an adequate and clear view. In addition, a lubricated intubation stylet (Portex Tracheal Intubation Stylet, SIMS Portex Limited, Hythe, Kent, UK) was inserted into an age-appropriate standard or RAE tracheal tube (ETT) with or without a tracheal cuff. Care was taken to avoid protrusion of the stylet tip beyond the distal orifice of the tracheal tube.

After placing the patient's head in a stabilization ring, the best laryngoscopic views obtained by conventional direct laryngoscopy without MILNS (procedure A) and with MILNS (procedure B) were assessed by the intubator and the investigator using the classification of Cormack and Lehane.[13] An additional assistant, positioned opposite the intubator, performed the MILNS. Subsequently, the laryngoscope was removed and the patient ventilated again by mask.

In a second step (procedure C), while maintaining MILNS, the intubator inserted the tip of the AVIL blade around the tongue into the oropharynx. Then the tongue was lifted by the AVIL tip until the video display revealed a full view of the vocal cords (Fig. 2). If this manoeuvre did not reveal an adequate glottic view on the monitor, the operator was allowed to gently lift the epiglottis with the AVIL tip. While maintaining an adequate monitor view of the cords, the styletted and distally angled (~45°) ETT was guided from the right corner of the mouth to the distal blade tip. As soon as the tracheal tube tip became visible on the monitor, it was guided into the larynx. After the ETT tip had passed through the vocal cords, the stylet was removed from the ETT and the ETT was advanced into the trachea. External laryngeal manipulation was not applied during any of the three intubation procedures. The final position of the ETT in the trachea was adjusted according to the black depth marking on the ETT or the position of the ETT cuff as visualized on the video display. Correct tracheal ETT placement was further confirmed by chest auscultation and capnography.

All intubations were performed by four residents or by six nurse anaesthetists with varying experience in anaesthesia. Every participant received brief instructions before the study but had no previous training on the use of the AVIL. Each participant performed tracheal intubation on six or more patients.

The time from insertion of the AVIL into the oral cavity until achievement of an adequate monitor view of the vocal cords was recorded as T_1. Total intubation time to final placement of the tracheal tube was defined as T_2. Intubation was considered a failure if the ETT was placed in the oesophagus or if arterial oxygen saturation dropped to less than 94% during intubation. Difficulties attributed to use of

Table 1 Number of laryngoscopic views obtained during direct laryngoscopy (procedure A), direct laryngoscopic views with MILNS (procedure B), and monitored laryngoscopic views (classification Cormack and Lehane)[13] provided by the angulated video-intubation laryngoscope during tracheal intubation with MILNS (procedure C)

Patients	**All**			**0 to <4 yr**			**4 to <8 yr**			**8 to <12 yr**			**12 to 18 yr**		
Procedure	**A**	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**
Grade I	86	14	98	27	10	30	21	4	23	26	0	30	12	0	15
Grade II	12	37	2	2	13	0	2	14	0	5	8	1	3	2	1
Grade III	2	47	0	1	7	0	0	5	0	0	22	0	1	13	0
Grade IV	0	2	0	0	0	0	0	0	0	0	1	0	0	1	0

the angulated video-intubation laryngoscope during intubation, and problems regarding the insertion of the ETT into the trachea were recorded. After completing the procedure, participants had to estimate the subjective degree of difficulty (DOD) in establishing an adequate monitor view of the cords with the AVIL (DOD_1), and of the endoscopic insertion of the ETT into the trachea (DOD_2), on a 10 point Likert-scale ranging from 1 (very simple) to 10 (very difficult).

Statistical analysis

We compared laryngeal visibility in the three procedures using Fishers' exact test. Logistic regression analysis was employed to identify variables that increased the risk of an impaired direct laryngoscopic view during MILNS or the improvement of laryngoscopic view obtained with the AVIL during MILNS. Possible variables included patient characteristics (age, sex, weight, and height), the blade used (Miller *vs* Macintosh) and experience of the operator (nurse *vs* resident, years of experience in anaesthesia, number of previous AVIL procedures during this study).

Time until successful visualization of the cords (T_1) and until final intubation (T_2) were compared across groups (e.g. nurses *vs* residents) by the unpaired Student's *t*-test. Multivariable regression analyses were used to identify variables associated with T_1 and T_2. These independent variables included: patient characteristics, experience of the intubator, subjectively perceived difficulty, number of intubation attempts (learning curve), and best direct laryngoscopic view with or without MILNS. In a separate regression analysis, we investigated possible associations between the aforementioned variables and subjective difficulty.

All tests were two tailed. A type I error probability of <0.05 was considered to indicate statistical significance. Analyses were carried out using the SAS software package (Version 6.12, SAS Inc., Cary, NC, USA).

Results

We enrolled 100 paediatric patients (mean age 7.2 (SD 4.5) yr, interquartile range 3.2–10.3 yr). Direct and monitored laryngoscopic views obtained during the different procedures (A, B, C) are summarized in Table 1.

The MILNS procedure was more likely to impair laryngoscopic visualization in older patients than in younger patients (Table 1). After controlling for the age of the patient ($P=0.001$), no other variable was significantly associated with the degree of impairment of visualization by the MILNS procedure (sex, weight and height, nurse *vs* resident, years of experience in anaesthesia, type and size of blade used; all $P>0.15$). Likewise the degree of improvement by optical visualization with the AVIL was positively associated with age ($P=0.001$), but no other variable (all $P>0.2$).

MILNS significantly impaired visualization of the larynx (Fisher's exact test, two-tailed, $P<0.001$). Video-assisted visualization under MILNS provided better visualization than unrestricted direct laryngoscopy (Fisher's exact test, $P=0.003$). Two patients, in whom direct laryngoscopy under MILNS revealed a Grade III and Grade IV view, respectively, required direct elevation of the epiglottis with the AVIL tip to obtain an adequate monitor view of the vocal cords (Grade I and Grade II, respectively).

Tracheal intubation with the AVIL was successfully performed in all patients. Intubation time (T_1) ranged from 8–45 s (mean 14 (SD 5.4); median 16.5) and total intubation time (T_2) ranged from 19–75 s (mean 35 (13.4); median 32). None of the patients suffered from arterial desaturation or oesophageal intubation during the intubation procedure. Visual positioning of the ETT in the trachea using the monitor was possible in 86 patients. In two patients visual ETT positioning was impaired by lens fogging and in 12 patients the RAE tubes used did not have a cuff or a black depth marking to adjust the final tracheal tube position.

No problems were reported with the endoscopic cable leading from the AVIL to the bedside monitor system. Fogging of the distal lens occurred in 12 patients, and soiling of the lens by secretions in three patients. In six patients, the AVIL had to be transiently removed for lens cleaning. In 21 patients, the angle of the styletted ETT had to be readjusted because of limited ETT manoeuvrability.

Although the angulated video-intubation laryngoscope successfully provided an adequate view of the cords in all patients aged from 3 months to 18 yr, operators considered that the blade was too long. This led to too deep an initial insertion of the blade, particularly in infants and smaller children

Crude analysis revealed that residents (40 intubations) needed more time to obtain visualization than nurses (60 intubations) (mean 16.3 (6.9) *vs* 12.9 (3.7) s; *t*-test P=0.007) and took longer to intubate (mean 38.0 (14.3) *vs* 32.2 (12.3) s; *t*-test P=0.039). In the multivariable model, additional factors that were significantly related to time to visualization (T_1) were: perceived difficulty of visualization, and years of experience in anaesthesia. Variables that were associated with intubation time (T_2) were time until visualization and the need to rebend the ETT tube. The direct laryngoscopic score with MILNS was not associated with time to intubation using the AVIL. Neither the required time to visualization (r=–0.1, P=0.32) nor intubation time (r=–0.13, P=0.13) was associated with prior experience with the video-assisted procedure. However, the more procedures operators had performed, the less difficulties they observed (r=–0.3, P=0.002). Failure to intubate the trachea within 30 s of beginning the procedure (n=53, 53%) was related to the need to adjust the angle of the ETT tip (odds ratio=6.8, 95% CI: 1.9–24.3). No other externally observable variable (resident or nurse, age of patient, weight, size of tube) showed a significant association.

Mean estimated degree of difficulty for video-laryngoscopic visualization of the larynx (DOD_1) was 2.9 (1.2) (median 3) and 3.7 (2.1) (median 3) for video-assisted ETT insertion (DOD_2). As expected, the subjective perception of the difficulty to visualize or to intubate correlated strongly with time to visualization or time to intubate, respectively.

Discussion

Our main finding was that the AVIL significantly improved the laryngeal view in infants and children in whom cervical spine immobilization impaired direct visualization of the vocal cords. Intubations were successfully performed in all patients by intubators without prior experience of the technique.

The AVIL combines the advantages of improved visualization from an angulated or curved ‘optical’ laryngoscope blade (Siker, Huffmann, Belscope, Bullard)[14–18] with video-transmission of the view from the blade tip to a monitor.[19] In contrast to the Belscope or the Bullard laryngoscope, the AVIL is mainly used for gently lifting the tongue without the need to directly elevate the epiglottis by passing the blade tip beneath it. This reduces the risk of mechanical trauma to the epiglottis and of soiling of the lens, should blood and secretions be present between the epiglottis and the posterior pharyngeal wall. The use of a thin, lightweight endoscopic cable instead of a video camera head and additional light cable facilitates handling of the device. The video-assisted intubation technique, combining laryngoscopy with the use of a styletted tube is almost a conventional manoeuvre, which can be performed without additional skilled assistance or extensive patient preparation. The familiarity of the technique is demonstrated by the high intubation success rate, low estimated degree of difficulty, absence of an objective learning curve (as measured by time to visualization or time to intubation), and clinically acceptable intubation times.

The fact that nurses and resident anaesthetists without any prior experience in paediatric fibre-optic intubation were able successfully to intubate a child with a Grade III laryngoscopic view underscores the potential usefulness of the device in such circumstances. The better performance by nurses was not clinically relevant (mean difference in intubation time 5.8 s). It may be related to the longer experience of nurses in paediatric anaesthesia compared with resident anaesthetists, who are scheduled to paediatric anaesthesia during a 6-month period only.

Although an adequate monitor view of the cords was obtained within a short time period (mean 15 s), insertion of the ETT into the trachea was significantly delayed in some patients by the limited manoeuvrability of the tracheal tube within the oropharynx, which made it necessary to re-adjust the angle of the ETT tip. This problem can be partly overcome by directing the ETT from the lateral corner of the mouth, which increases the sagittal manoeuvrability of the ETT tip. However, the lack of manoeuvrability limits the use of the video-assisted technique in patients with reduced mouth opening. It is possible that in such circumstances the ETT would be more easily guided into the trachea with the use of a directional intubation stylet, or by a non-malleable intubation stylet attached to the AVIL as used in the Bullard laryngoscope.[20]

The observed intubation times were longer then those reported by Nolan and Wilson, who used the gum elastic bougie intubation technique in patients with potential cervical spine injuries (median 25 s; all within 45 s).[10] There is no doubt that tracheal intubation is more rapidly achieved with direct laryngoscopy and the gum elastic bougie, but the procedure is a blind technique in some cases, with the associated risk of oesophageal intubation, repeated intubation attempts or even failed intubation. It should be noted that, in contrast to the study by Nolan and Wilson, operators in this study had no prior experience with the AVIL. The intubation times achieved should not therefore be directly compared. A strategy that was not explored in this study is the combination of the AVIL with a gum elastic bougie. It is conceivable that this would further facilitate rapid intubation of the trachea with the additional advantage of not having to remove the gum elastic bougie until the ETT tip is placed in its final position.

As the presented technique closely resembles conventional laryngoscopy and did not jeopardize the patients' safety, the technique could be regularly used for training during routine anaesthesia. The AVIL, which does not include control wires and working channels, is much cheaper (estimated cost: £1200), less susceptible to damage during handling and is easier to clean than sophisticated fibre-optic bronchoscopes. This allows more frequent use of the angulated video-intubation laryngoscope for training than flexible fibre-bronchoscopes.

The AVIL is cleaned in the same way as flexible fibrebronchoscopes, namely by washing or immersion as well by sterilization using ethylene oxide, except that cleaning the working channels and leak testing do not have be performed with the AVIL. Cleaning of airway devices has become an increasing problem and disposable laryngoscope blades have been proposed to prevent the transmission of infection.[21] The use of disposable AVIL blades, in which the optic channel is closed distally by a small membrane, would protect the inserted fibrescope from contamination by a patient, so that the fibre-optic part could be immediately reused.

Fogging of the lens and interference by secretions are problems inherent to fibre-optic intubation devices and resulted in prolonged intubation times in six of our 100 patients in this study. Fogging of the lens may be prevented by the use of appropriate anti-fog agents applied by fine gauze. The incidence of lens soiling can be reduced by oropharyngeal suction before insertion of the laryngoscope blade. Carefully guiding the AVIL around the tongue instead of blindly placing the device into the oropharynx further helps to prevent lens contamination with secretions or blood. Oxygen flushing at the distal lens tip, as used in the Bullard laryngoscope, might help to prevent fogging and soiling of the lens by secretions, and also prolongs available time for intubation by apnoeic oxygenation.[20 22 23] Oxygen insufflation through the fibre-bronchoscope is not recommended during fibre-bronchoscopic intubation because of the risk of gastric or pulmonary barotrauma when the scope enters the upper oesophagus or becomes sealed within the trachea.[24 25]

Although different sized AVIL-blades would be beneficial, the device was successfully used in patients aged from 3 months up to 17 yr, in whom at least two or three sizes of flexible fibre-bronchoscope would have been required. A further benefit of the device over blind railroading of the ETT over a gum elastic bougie or a flexible fibrebronchoscope is the provision of a view of the ETT passing between the vocal cords. On the other hand, flexible bronchoscopes provide unrestricted manoeuvrability and allow suctioning of secretions and blood from the airway – an advantage over the AVIL technique. The dependence on a video-endoscopic monitor system limits the use of the AVIL and thus the technique is currently not suitable for use at an accident site. However, the availability of miniature video screens as reported by Popat and Lehane will broaden the application spectrum.[26]

The angulated video-intubation laryngoscope will not replace flexible fibre-bronchoscopic intubation in all cases of difficult direct laryngoscopy, but the AVIL provides rapid endoscopic assistance if unanticipated difficulties arise during direct laryngoscopy. In paediatric patients with cervical spine instability requiring immediate emergency tracheal intubation under MILNS, it provides a simple and effective tool for the anaesthetist who is not familiar and/or not equipped with paediatric fibre-optic bronchoscopes The usefulness of the device for children and adult patients with genuine difficult tracheal intubation and comparison to other endoscopic intubation techniques requires further investigation.

A caveat of our study design was to refrain from applying optimal external laryngeal manipulation. This might have improved visualization of the larynx during the MILNS procedure. However, the study design was chosen to provide an ethically acceptable simulation of patients with poor laryngeal visibility during conventional intubation.

In conclusion, the angulated video-intubation laryngoscope effectively facilitated tracheal intubation in children, in whom immobilization of the head and neck impaired direct visualization of the larynx. The intubation technique is simple and closely resembles conventional intubation. Intubators therefore become familiar with it after only very brief training. The efficacy of the AVIL for routine direct laryngoscopy and for genuinely difficult intubation in children and adults needs to be elucidated and to be compared with other endoscopic intubation techniques.

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BJA

LABORATORY INVESTIGATIONS

Temporal dynamics of lung aeration determined by dynamic CT in a porcine model of ARDS

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We used dynamic CT to identify two different time constants of lung aeration and their individual contribution to the total increase in cross-sectional lung area in healthy and experimentally damaged lungs. In five healthy pigs, inflation and deflation between 0 and 50 cm H_2O was imposed during dynamic (250 ms/image) CT acquisition, and repeated after experimental lung injury by saline lavage. The fractional areas of density ranges, which represent aerated lung parenchyma, were determined planimetrically, and their time for expansion during the manoeuvre was fitted using a bi-exponential model. Thus, two compartments, their sizes, i.e. their relative contributions to lung area aerated by the manoeuvre, and their specific time constants (τ) were sought. Healthy lungs were characterized best by a one-compartmental behaviour with one τ only, both during inflation (median τ=0.5 s; range 0.4–0.6 s) and deflation (1.2 s; 1.1–1.3 s). In damaged lungs two compartments were found both during inspiration and expiration, with 86% (78–87%) of the recruitable lung area following a short τ of 0.5 s (0.5–0.6), and 14% (13–22%) following a longer τ of 9.1 s (8–16.8 s) during inflation. During expiration, damaged lungs had a short τ of 0.8 s (0.5–1.0 s) for 94% (84–100%) of deflated lung area, and a longer τ of 26.5 s (7.1–34.3 s) for 6% (0–16%). We conclude that dynamic CT indicates the relative size and temporal behaviour of functional compartments in normal and abnormal lungs. Our findings suggest that after lung damage, cyclic ventilation with inspiratory periods of <10 s duration will not achieve maximum recruitment for a chosen inspiratory pressure. In ARDS, the short expiratory τ predisposes to atelectasis formation if expiratory times are >1 s.

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In acute lung injury, maldistribution of ventilation and perfusion is the most frequent cause of gas exchange impairment. The best settings for mechanical ventilation are based on empirical rules and trials of treatment such as the response of gas exchange to PEEP. Clinical progress is followed by measurement of blood gases, respiratory mechanics and by chest x-ray. Static chest CT can be used to stage ARDS and detect complications (e.g. barotrauma), but is not used to adjust ventilation.[1]

A recent CT acquisition technique, called dynamic multiscan CT, allows continuous image acquisition with a temporal resolution of 250 ms. This superior resolution allows changes in radiologic attenuation of the lung during mechanical ventilation to be followed. Neumann and colleagues investigated the temporal behaviour of poorly aerated lung regions and atelectases during inspiration and expiration in pigs with experimental lung damage. Using a monoexponential relationship, they described the kinetics of mean radiologic density of the lung (mean lung density, MLD) and of two density ranges describing poorly aerated lung and atelectasis.[2] We considered that although aeration of the healthy lung may have one-compartmental behaviour,

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aeration of damaged lungs may be better described by considering more than one compartment. To obtain maximum sensitivity for ventilation-induced changes in aeration, we analysed those lung density ranges which had shown the greatest area change with inspiratory and expiratory manoeuvres in a previous study of similarly treated animals (see Fig. 5).[3] To prove our hypothesis, we used an experiment to allow us to discriminate different τ: (1) the repeated lavage model, which has been described as a model for lung collapse and recruitment phenomena;[2] and (2) rectangular airway pressure steps between ZEEP and 50 cm H_2O, in order to allow both atelectasis formation and nearly complete recruitment.

Materials and methods

Instrumentation

With Animal Care Committee approval, five pigs (26.8 (SD 1.6) kg) were anaesthetized (piritramide 1.2 mg kg^{-1} i.v.; thiopentone 10–15 mg kg^{-1} i.v.) and ventilated via a tracheal tube (ID 7.0 mm), in volume-controlled mode with 15 cycles min^{-1}, a ratio of inspiration:plateau:expiration=25:10:65%, a PEEP of 5 cm H_2O, and a fractional inspiratory oxygen (FI_{O_2}) of 1.0 (Servo 900C, Siemens, Germany). The expired tidal volume was set to 12 ml kg^{-1} and adjusted to keep the end-tidal carbon dioxide concentration between 35 and 40 mm Hg. Anaesthesia was maintained by continuous i.v. infusion of piritramide (2 mg kg^{-1} h^{-1}) and thiopentone (10 mg kg^{-1} h^{-1}). We measured ECG, and the femoral vessels were exposed to insert arterial central venous and pulmonary artery catheters. Intravascular pressures (Sirecust 404-1, Siemens, Germany), arterial blood gases and acid–base status (Paratrend 7, Diametrics Medical Ltd, UK) were measured continuously. For calibration of the Paratrend Monitor routine blood gas measurements from arterial and mixed venous blood were made (ABL 500/OSM 3, Radiometer Copenhagen, Germany). After instrumentation was completed, the animals were positioned in supine position in the CT scanner (Somatom Plus 4, Siemens, Germany).

Study procedure

Baseline values of haemodynamics, blood gases, and acid–base status were obtained. Two scout views were taken during end-inspiratory and end-expiratory breathholds and a transverse, supradiaphragmatic slice was defined by a reference scan. Thus, a fixed table position was defined which allowed the visualization of lung parenchyma between the apex of the heart and the diaphragm, both during inspiration and expiration.

Airway pressure step manoeuvres were performed with healthy lungs and again after surfactant-depletion by repeated lavage of the lungs. Lung lavages were performed 9±1 times with 1 litre of isotonic Ringer's solution.[4] Inotropic support was provided by continuous infusion of 3±2 μg kg^{-1} h^{-1} epinephrine after lung lavages.

To generate a quasi-rectangular increase or decrease in airway pressure, the respirator was switched to its CPAP mode, and the CPAP level was increased swiftly in one step from end expiration (ZEEP=0 cm H_2O) to 50 cm H_2O or from CPAP of 50 cm H_2O to ZEEP, respectively. The CT acquisition was started 5 s before the airway pressure step and continued for at least 30 s after the step change. Volume-controlled ventilation was resumed afterwards, until baseline haemodynamics and blood gases were restored.

CT acquisition parameters

In all dynamic multiscan CT acquisitions, the tube voltage was set to 120 kV and the tube current to 110 mA. A matrix of 512×512 and a slice thickness of 1.0 mm was used. Images were reconstructed using the high-resolution algorithm. Total rotation time of the x-ray tube was 750 ms allowing for an overlapping temporal increment, i.e. an effective temporal resolution, of 250 ms.

Quantitative analysis of CT scans

In each lung image, the total lung area was determined semi-automatically using a dedicated software (Pulmo-Software®, Siemens, Germany). An interactive correction was carried out if the total lung area resulting from the automatic segmentation did not represent the anatomical lung area. Such errors occurred predominantly in damaged lungs. The boundaries of the lung were defined by the ribs, the aorta, and the heart. All segmentations were performed by one investigator to avoid operator-related variation. The total lung area (density range from −1024 to +200 HU) was automatically divided into fractional areas of defined densities.[3] The density range from −910 to −700 HU was used to describe aerated lung parenchyma in healthy porcine lungs. The range from −910 to −300 HU represented aerated tissue in the lavaged lungs model. For each density range, the corresponding relative lung area was evaluated planimetrically.

Radiological interpretation

To verify the quantitative analysis by density ranges, every image series was evaluated by a board-certified radiologist (H.-U.K.) for the following criteria: general lung aeration, presence of atelectasis, and a ventral-to-dorsal gradient. An image-by-image evaluation was done to describe the temporal evolution of these criteria.

Identification of lung compartments, their time constants (τ) and fractional sizes (A)

The time behaviour of a specific density range during inflation or deflation was analysed under the a priori assumption of two-compartmental behaviour. The change in aeration (air content) of one homogeneous compartment in response to a rectangular airway pressure increase or decrease can be described by a mono-exponential wash-in or wash-out function, respectively:[5]

$$V_{(t)} = V_0 * e^{-(t/\tau)}$$

(V, expired volume; τ, time constant).

In this study, τ was derived from the temporal dynamics of the area of a defined density range in subsequent CT images. In the following, ΔA denotes the lung area, which becomes aerated by the airway pressure increase from ZEEP, or collapses during the airway pressure decrease to ZEEP. The lung area at ZEEP was defined as the baseline for the aeration manoeuvre (and as the endpoint of collapse, respectively), and was not taken into account for this analysis. To separate the two time constants τ, the increase or decrease of aerated lung area in response to the airway pressure change was fitted by a least-squares fitting procedure using a bi-exponential relationship, i.e.,

$$\Delta A_{(t)} = \Delta A_1 * e^{-(t/\tau_1)} + \Delta A_2 * e^{-(t/\tau_2)}$$

In this relationship, ΔA_1 represents the fraction of ΔA, which follows a time constant τ_1. ΔA_2 represents the fraction of ΔA with a temporal behaviour characterized by τ_2.

First, the temporal behaviour of the area of the predefined density range was plotted. The bi-exponential equation (above) was then introduced as user-defined fitting function. Data points were fitted with the software package Origin® (Origin 4.0, Microcal Software Inc., USA). As the fitting procedure requires a selection of starting values for the parameters, we chose the following parameters, which gave reproducible results in simulation curves: ΔA_1=80%, ΔA_2=20%, τ_1=1 s, and τ_2=10 s. These settings were applied to all data sets, i.e. before and after lung damage, and gave a satisfactory goodness of fit (chi-squared=2.06 (0.75); mean (SD) for all fits performed). An example of a fit result is given in Figure 1.

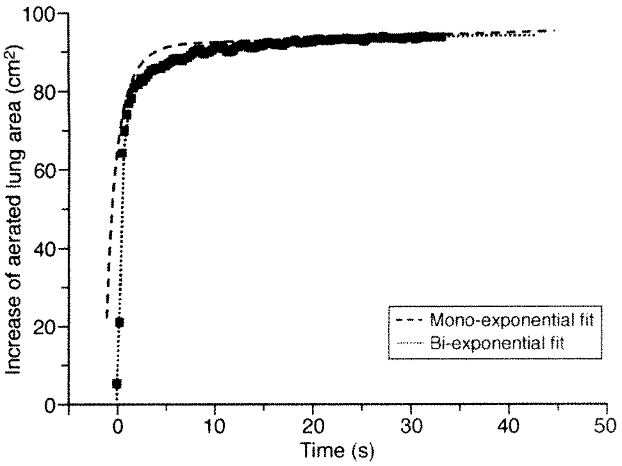

Fig 1 Example of least-squares fit procedures. Increase of aerated lung area (in cm^2) following an airway pressure increase from 0 to 50 cm H_2O (animal no. 5; lavage ARDS). The increase of aerated area (representing alveolar distension as well as recruitment) described by a mono-exponential fit to the data yields a τ of 11.2 s, whereas a bi-exponential fitting procedure allows discrimination of two different τ of 0.5 and 8 s, and a better fit.

Depending on the individual contribution of each compartment to the aeration process, a one- or a two-compartmental behaviour of lung aeration was defined. Two compartments were considered present if $\Delta A2$ exceeded 5% of ΔA, whereas a compartment size of ≤5% was neglected.

Haemodynamics and gas exchange measurements

Before lung damage and after stabilization after repeated lung lavages, we recorded aortic and central venous pressures, and cardiac output. For assessment of gas exchange, arterial and mixed venous blood gases were measured.

Results

We measured five animals with healthy lungs and four animals with lavaged lungs. One animal died during lung damage. Haemodynamic and gas exchange values before and after lavage of the lungs are shown in Table 1. Lavage caused a mean oxygenation index (Pa_{O_2}/FI_{O_2}) of 61. Haemodynamic measurements after lung damage were made during low-dose inotropic support.

Radiological interpretation

Healthy lungs

At end-expiration, an antero-posterior increasing gradient of attenuation was seen, and only a small amount of atelectasis could be observed, whereas at end-inspiration the lung

Table 1 Baseline haemodynamics and acid–base status before and after induction of the lavage-ARDS model, given in mean (SD). SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; CVP, central venous pressure; CO, cardiac output; Pa_{O_2}, arterial oxygen partial pressure; Pa_{CO_2}, arterial carbon-dioxide partial pressure; HCO_3^-, standard bicarbonate

Parameter	**Healthy lungs (n=5)**	**Lavage-ARDS (n=4)**
SAP (mm Hg)	109 (12)	94 (9)
DAP (mm Hg)	69 (12)	46 (9)
MAP (mm Hg)	85 (14)	65 (7)
CVP (mm Hg)	4.3 (3)	3 (1.4)
CO (litre min^{-1})	2.6 (0.1)	4.8 (3)
Pa_{O_2} (mm Hg)	513 (5.1)	61 (13.4)
Pa_{CO_2} (mm Hg)	37 (2.9)	53 (15.5)
pH	7.49 (0.04)	7.19 (0.19)
HCO_3^- (mmol litre^{-1})	27.6 (3.59)	18.2±7.35
Base excess	6.25 (4.03)	-11 (8.77)
Haemoglobin concentration (g dl^{-1})	7.9 (1.2)	10 (2.8)

parenchyma appeared completely aerated (see Fig. 2A–C). Only a very small amount of over-expansion was noticed. During airway pressure changes, lung density changed homogeneously.

Lavage ARDS

At end-expiration, large portions of the lung were atelectatic, predominantly in the dependent lung regions. During inflation, lung density in already aerated lung areas decreased first, followed by a reduction of atelectasis (see Fig. 3A–C). At end-inspiration, a marked and antero-posterior gradient of increasing density gradient was accompanied by a significant number of regions with signs of over-expansion. During deflation, a fast reappearance of atelectasis paralleled the increase of lung density over the entire cross-sectional slice. Some atelectasis persisted throughout all images.

Aeration process in healthy lungs

Inflation

Healthy lungs had a one-compartmental behaviour, with a median τ of 0.5 (range 0.4–0.6 s).

Deflation

A deflation process with a single fast compartment was present in all animals, with a time constant of 1.2 s (range 1.1–1.3 s). In only one of five animals a second, longer τ of 4.5 s was evident, which comprised 7% of the total ventilated lung area. In four of five healthy animals, the deflation process fulfilled the prospectively defined criterion of a fast one-compartmental behaviour.

Lavaged lungs

Inflation

Here, a short time constant of 0.5 s (range 0.5–0.6 s) was detected in 86% (range 78–87%) of the lung area inflated by the manoeuvre. The second, longer τ of 9.1 s (range 8–16.8 s) was found in 14% (range 13–22%) of the inflation area (see Fig. 4A).

Deflation

A short τ of 0.8 s (range 0.5–1.0 s) was found in 94% (84–100%) of lung area deflated during the manoeuvre, and a longer τ of 26.5 s (7.1–34.3 s) governed a slow compartment, which comprised 6% (0–16%) of the deflated area. Thus, during expiration, ARDS lungs showed a bi-compartmental behaviour in three of four animals, whereas

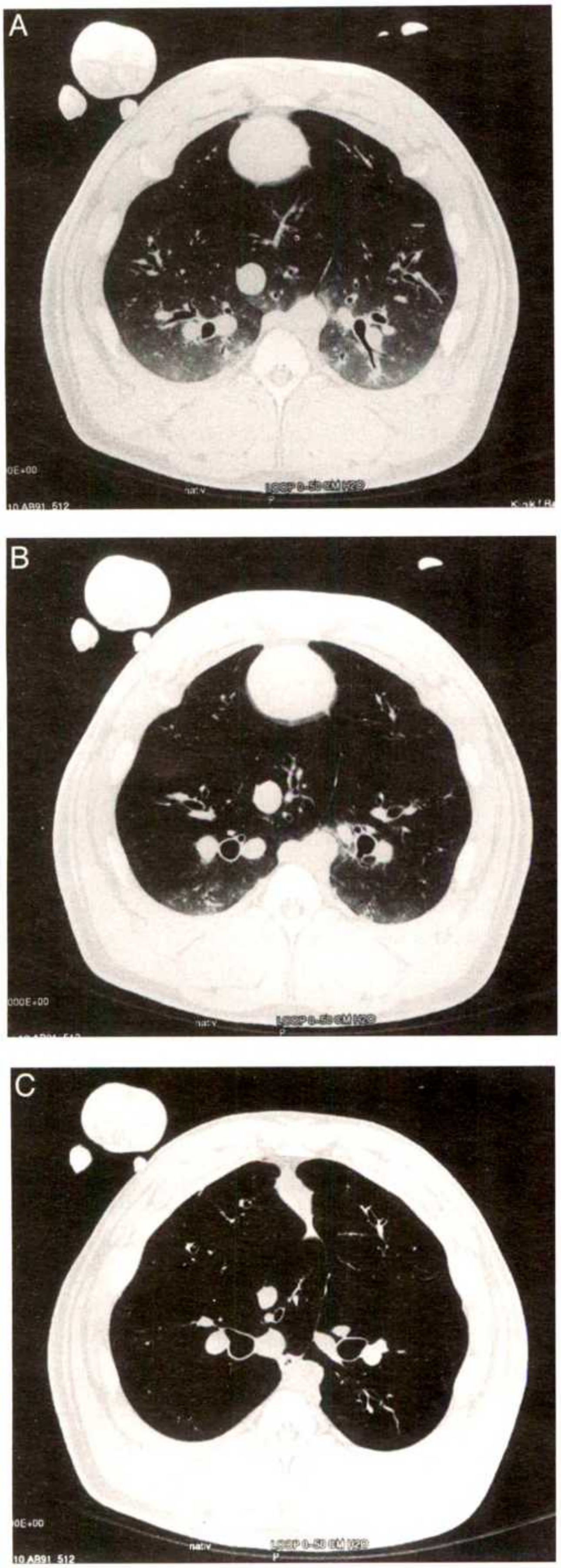

Fig 2 Transverse supradiaphragmatic CT scans of healthy lungs during airway pressure increase from 0 to 50 cm H_2O. (A) At end-expiration, an antero-posteriorly increasing density gradient is visible. (B) After 3 s of CPAP maintained at 50 cm H_2O, lung parenchyma appears almost homogeneous, with only slightly increased lung density in basal lung areas. (C) Lung parenchyma appears homogeneously aerated 31 s after the airway pressure increase to 50 cm H_2O CPAP.

Table 2 Lung compartments assessed by multiscan CT before and after lavage ARDS induction: co-existing time constants and correspondent compartment size. τ 1, short time constant in s; τ 2, long time constant in s; fractional area 1, compartment size of τ 1 in per cent which becomes aerated by the airway pressure increase from ZEEP, or collapses during the airway pressure decrease to ZEEP; fractional area 2, compartment size of τ 2 in per cent which becomes aerated by the airway pressure increase from ZEEP, or collapses during the airway pressure decrease to ZEEP

Healthy lungs (*n*=5)	**Inflation**				**Deflation**			
Animal	τ 1	τ 2	Fractional area 1 (%)	Fractional area 2 (%)	τ 1	τ 2	Fractional area 1 (%)	Fractional area 2 (%)
1	0.5	–	100	0	1.2	–	100	0
2	0.4	–	100	0	1.3	–	100	0
3	0.4	–	100	0	1.1	–	100	0
4	0.5	–	100	0	1.2	4.5	93	7
5	0.6	–	100	0	1.3	–	100	0
Median	0.5		100		1.2	(4.5)	100	(0)
Min/max	0.4/0.6				1.1/1.3		93/100	0/7

ARDS lungs (*n*=4)	**Inflation**				**Deflation**			
Animal	τ 1	τ 2	Fractional area 1 (%)	Fractional area 2 (%)	τ 1	τ 2	Fractional area 1 (%)	Fractional area 2 (%)
2	0.6	8.1	86	14	0.5	7.1	84	16
3	0.5	16.8	78	22	0.8	26.5	94	6
4	0.5	10.0	87	13	0.8	–	100	0
5	0.5	8.0	86	14	1.0	34.3	93	7
Median	0.5	9.1	86	14	0.8	26.5	94	6
Min/max	0.5/0.6	8/16.8	78/87	13/22	0.5/1.0	7.1/34.3	84/100	0/16

only one of four animals showed a fast, one-compartmental deflation behaviour

Individual data for all animals are listed in Table 2.

Discussion

We wished to compare ventilation and recruitment processes in healthy lungs and in the lavage model of ARDS using a dynamic CT-based method. We hypothesized that we might identify two different compartments, on the basis of their temporal behaviour, and their contribution to total lung aeration (i.e. distension of already open as well as recruitment of collapsed alveoli) after lung damage by lavage.

In healthy lungs, the inflation and deflation processes are characterized best by a one-compartmental behaviour, whereas after lavage the co-existence of two compartments with clearly different τ was observed. A short inspiratory τ was found for 86% of the total lung area ventilated or recruited by the manoeuvre. The remaining 14% of finally aerated lung area inflated quite slowly with a long τ of about 10 s. In contrast, during expiration, 94% of the damaged lung collapsed very quickly with a τ of less than 1 s, compared with slower deflation with a τ of more than 1 s in the healthy lungs.

Radiological interpretation of the dynamic series of CT scans gave a more descriptive assessment of the temporal dynamics of lung aeration with ventilation and recruitment phenomena in ARDS.

During inflation, areas that were already filled expanded first, followed by a slow recruitment of atelectasis. Thus, the short τ in inspiration appeared to represent ventilation of already aerated alveoli, whereas the longer τ reflects recruitment of atelectatic areas.

During deflation, rapid collapse of large portions of lung parenchyma, with a rapid increase of atelectatic and hypoventilated dense lung areas, causes the short expiratory τ. The long expiratory τ in ARDS represents expiration from lung areas, which remain air-filled even at ZEEP.

In a similar animal model of ARDS, Wegenius and colleagues described a quantal behaviour of atelectatic lung detectable by CT. This behaviour is because surfactant-depleted alveoli are either fluid-filled and thus collapsed, or air-filled and open, but almost no intermediate states are present.[6] This theory is supported by our observation that only after lung damage, i.e. after development of widespread expiratory alveolar collapse, two-compartmental behaviour appears. During inflation, the short τ reflects inflation of open alveoli (i.e. a ventilation process), and the longer τ represents the slower opening of collapsed alveoli at their respective opening pressures, for example the recruitment process. During deflation, fast expiration of air is accompanied by the rapid formation of large atelectatic areas, which explains the large compartment with a short τ of <1 s.

As we aimed to develop a diagnostic method to characterize compartments of lung aeration in ARDS, we chose a lavage-induced form of lung damage to reproduce the ventilation and recruitment processes after surfactant-depletion according to Wegenius and colleagues.[6] The lavage model simulates only one aspect of ARDS, i.e. loss of surfactant.[7] In our study, the appearance of the CT images was consistent with the well-described radiological criteria for healthy lungs during general anaesthesia, and for lungs in an early stage of ARDS, respectively.[8 9] Images also closely resembled those published by Neumann and co-workers, who compared saline-lavage in pigs with ARDS induced by oleic acid and endotoxin administration, using dynamic CT.[2]

Various definitions of 'lung aeration', defined by densitometry of CT images, co-exist in the radiology literature. Neumann and co-workers used the increase or decrease of MLD to quantify the changing air content in serially acquired CT images.[10] MLD reduces the entire distribution function of density values, for example the attenuation histogram, in the lung to a single-number descriptor. Therefore, it will reflect not only the change of aeration in a lung region of interest, but also varying contributions of intravascular and extravascular water content. Temporal dynamics of MLD are, therefore, determined not by the processes of aeration (or collapse) alone, but by the net temporal behaviour of all density domains or compartments of a region together. A decrease in MLD may thus represent effects as different as recruitment, ventilation, overdistension, or even barotrauma. Such processes are, however, clearly discernible if, within the spectrum of attenuations, a density range is selected which is known to specifically reflect the effects of interest. We wished to detect rapid changes in parenchymal aeration, for example recruitment and ventilation, with high sensitivity, and not to compare absolute gas content of healthy and diseased lungs. Therefore, we studied aeration changes by following the temporal behaviour of specific density windows, which we had tuned to our animal model and imaging parameters in a previous study.[3] In the literature, a density range of –910 to –500 HU is used to detect aerated lung areas. In this previous study, airway pressure was increased and decreased in a stepwise manner (5 cm H_2O every 5 s) during dynamic multiscan CT. In healthy and lavaged lungs, the fractional area change of attenuation ranges of increasing bandwidth (constant lower threshold of –910 HU, higher threshold increasing from –800 HU to –200 HU in steps of 100 HU) was determined planimetrically and compared. We found a density window from –910 HU to –700 HU for healthy lungs, and from –910 HU to –300 HU for lavage ARDS to be most sensitive to airway pressure-dependent changes in lung aeration.[3] These response curves are shown

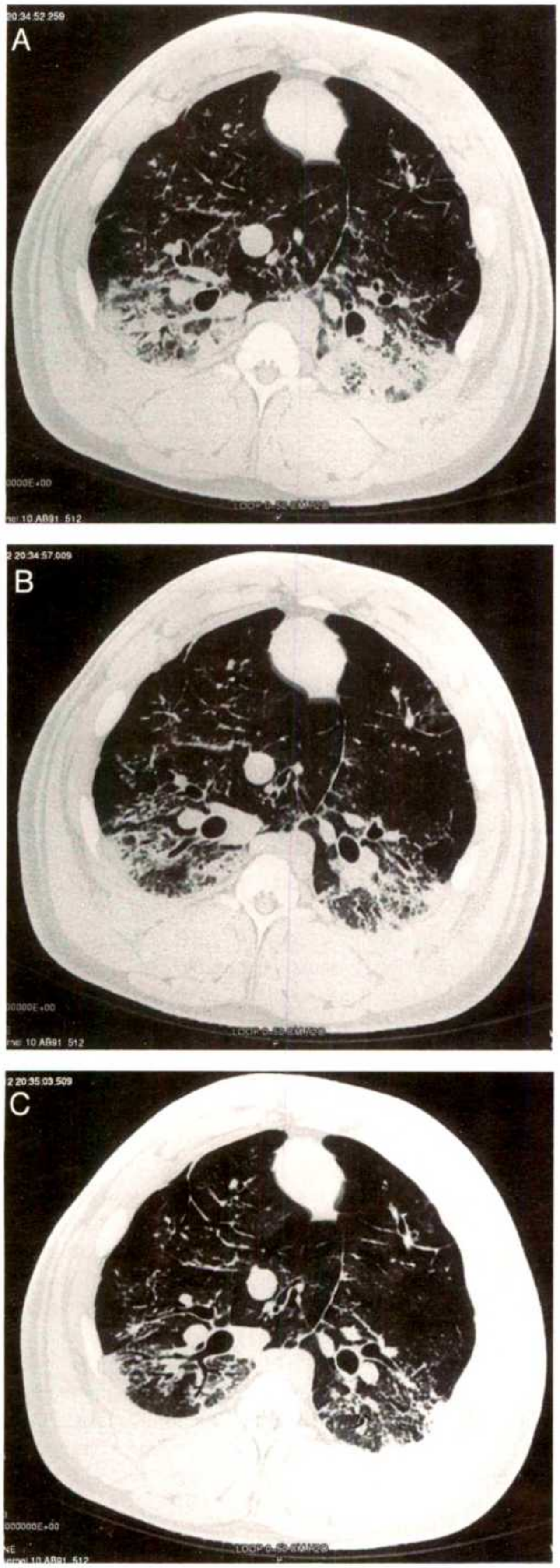

Fig 3 Transverse supradiaphragmatic CT scans of lavage-ARDS lungs during airway pressure increase from 0 to 50 cm H_2O. (A) At end-expiration, large areas of atelectatis and a marked antero-posterior density gradient can be observed. (B) After 3 s of CPAP maintained at 50 cm H_2O, a reduction of atelectasis is visible, although a marked density gradient remains. (C) At end-inspiration, 31 s after increase to 50 cm H_2O CPAP, the entire cross-sectional lung area appears aerated, although to a variable degree. Nevertheless, ground-glass opacities caused by increased lung water content persist. In the scans acquired subsequently, a slightly varying slice position can be noted as a result of a cranio-caudal motion of the lung during the manoeuvre.

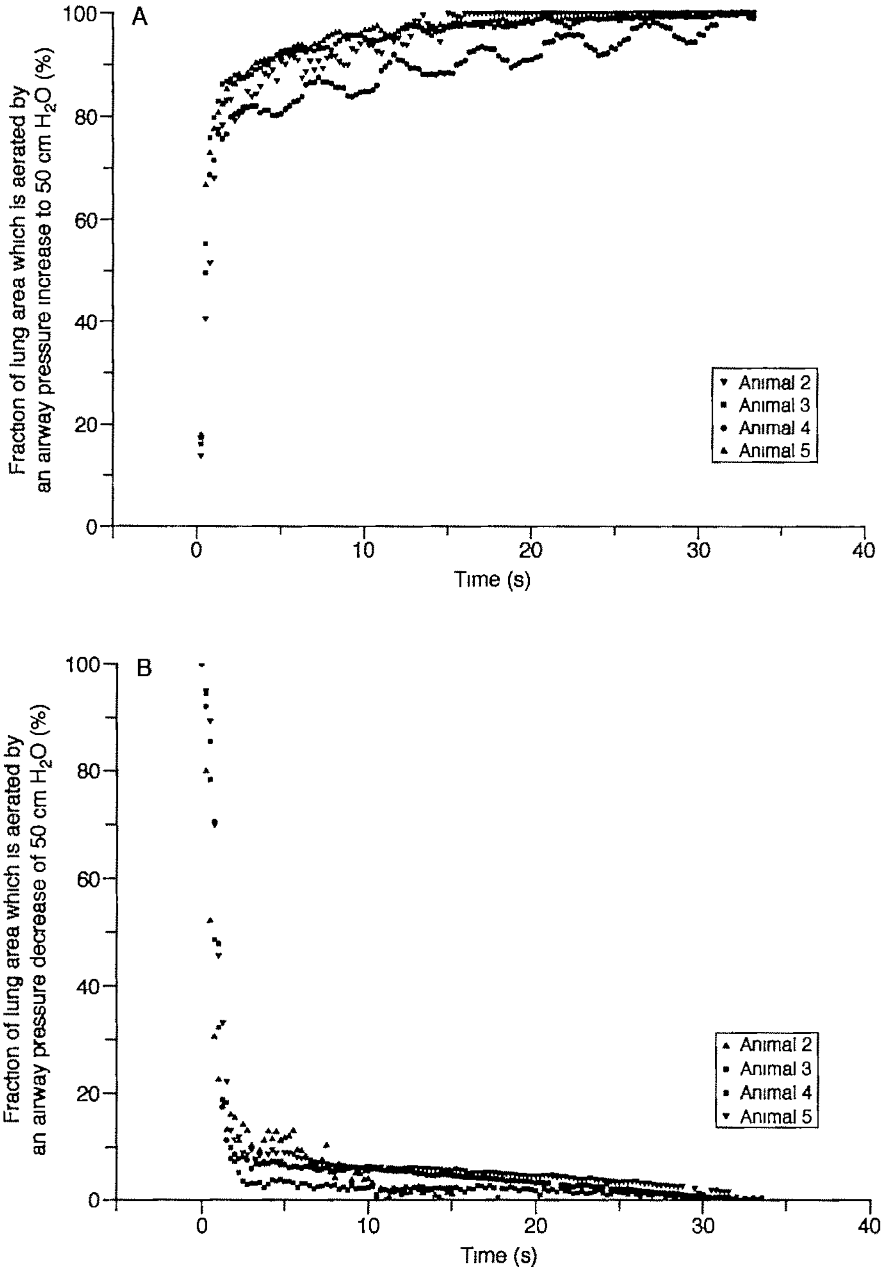

Fig 4 (A) Relative increase of aerated lung area after airway pressure increased from 0 to 50 cm H_2O in lavage ARDS. Aerated lung area (pixels with densities ranging from −910 to −300 HU) is expressed as fraction (in per cent), which becomes aerated from the airway pressure increase from ZEEP (B) Relative decrease of aerated lung area after airway pressure decreased from 50 to zero cm H_2O in lavage ARDS. Aerated lung area (pixels with densities ranging from −910 to −300 HU) is expressed as fraction (in per cent), which collapses from the airway pressure step-down to ZEEP. Individual animals are represented by different symbols.

in Figure 5. They are explained by the fact that after lavage a greater parenchymal water content causes ground-glass opacities which nevertheless respond strongly to aeration. Another way to assess aeration of lung tissue, which also avoids the shortcomings of regional analysis of MLD, is to calculate the total amount of air on a pixel-by-pixel basis as described by Puybasset and colleagues.[11] This approach translates, in a strictly proportional fashion, x-ray attenuation (in Hounsfield Units) into fractional gas content, and calculates absolute FRC from this and from the volume of voxels. To obtain volumetric data that are meaningful to the clinician, this technique requires static thin-section CT acquisition of the entire lung volume At present, however, fast dynamic assessment of multiple slices or even the entire lung volume is not yet technically possible. Once this is achieved, our technique will allow calculation of the compartmental distribution of the tidal volume and the pertinent time constants, similar to that of Puybasset and

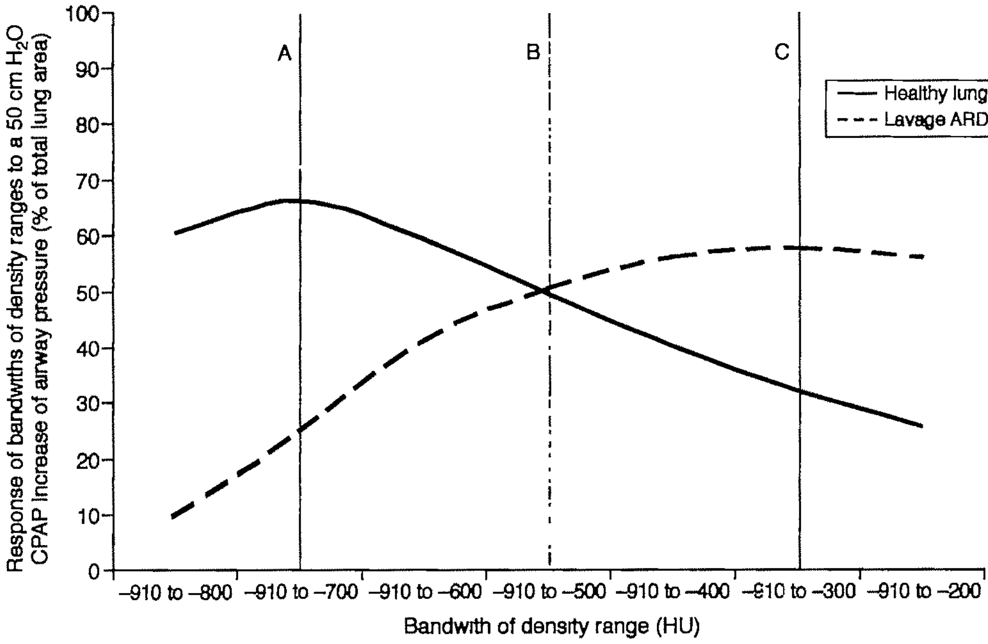

Fig 5 Increase in area (relative to endexpiration at ZEEP) of density ranges of growing bandwith (lower threshold −910 HU; upper threshold increasing from −800 to −200 HU), if a step-wise inspiratory manoeuvre is performed to a CPAP of 50 cm H_2O (data from Markstaller and colleagues[3]). The solid line describes the behaviour of density ranges in healthy lungs, the dashed line in lavage-ARDS lungs. In healthy lungs, sensitivity to changes in parenchymal aeration is already at the maximum for the density range from −910 to −700 HU (A), whereas in the lavage-ARDS model the range from −910 to −300 HU (C) is the most sensitive, encompassing all states of parenchymal aeration except overdistension. The response of the commonly used range (−910 to −500 HU) to inspiration is submaximal but similar for both healthy and lavaged lungs (B). Such an offset from the maximum would cause the analysis, in ARDS lungs, to miss some recruitment of atelectasis, whereas in healthy lungs, it is an unnecessary inclusion of cross-sectional area which does not respond to inspiration

colleagues. However, as our study was restricted to a fast dynamic but two-dimensional analysis of only one large transverse lung slice, attenuation was not transformed further into gas content in that slice, particularly because relative compartmental size and time constants are independent of such a transformation.

Neumann and colleagues evaluated the temporal dynamics of lung inflation and collapse with a fast CT technique, assuming a priori a one-compartmental behaviour of the lung. They found that both recruitment and collapse of lungs damaged with saline lavage, oleic acid and endotoxin-induced ARDS occurred mainly during the first 4 s. In lavage-ARDS, a longer τ (~2.0 s) was observed in expiration than in inspiration (~0.7 s).[2] Our results support these findings. These authors fitted their data to follow a mono-exponential relationship, and the contribution of our ‘slow’ compartment may have been underestimated by their choice of an upper CPAP level of ~40 instead of the 50 mbar we used. They concluded that in their experimental settings, expiratory times <0.6 s would be necessary to avoid cyclic alveolar collapse during mechanical ventilation, which is also supported by the findings of our study for the lavage-ARDS model.

In a related study of porcine oleic-acid-induced ARDS, Neumann and co-workers used several PEEP levels ranging from 10 to 25 cm H_2O and an inspiratory peak pressure of 15 cm H_2O above PEEP to determine the minimum PEEP level as well as the critical inspiratory and expiratory time to avoid lung collapse.[11] They found that a PEEP level >20 cm H_2O or an expiration time $\leq$0.6 s were required to largely prevent expiratory lung collapse. As the short deflation τ_1 in our ARDS series ranged between 0.4 and 1.0 s, we predict that reducing expiration time to $\leq$0.6 s would allow deflation of only about 60% of the fast compartment, causing FRC to increase, and would completely prevent collapse of the ‘slow’ compartment (τ_2 >7 s). However, whereas titration of PEEP or expiration times takes time and requires repeated assessments by blood gas analysis or CT, the technique to derive compartmental time constants of lung aeration from one rectangular CPAP manoeuvre may reduce the time to optimize the ventilation pattern in an individual ARDS patient.

Recently, electrical impedance tomography (EIT) has been introduced as another image-based technique to quantify regional lung aeration. Kunst and colleagues showed, that the lower and upper inflection point can be determined with EIT in porcine lavage ARDS lungs.[12] In contrast with dynamic CT, EIT can be used as a bedside technique without any radiation exposure. CT, on the other hand, allows much better temporal and spatial resolution. Further studies are necessary to compare these methods and their potential roles for clinical decision-making.

A current limitation of our technique is that the resolution of the CT data is only achieved in one cross-sectional slice of the lung. We selected a slice between apex of the heart and diaphragm, which allows a fair approximation of total ventilated lung area.[2 13] To reduce consecutive errors in planimetry and densitometry, the cross-sectional slice for image acquisition was determined by a scout view and a reference scan before each experiment. This slice definition was important to ensure that in every CT image only the lung parenchyma between the apex of the heart and the diaphragm was measured. Also, as the scanner table is immobile during the dynamic multiscan acquisition, this slice cannot be followed during inspiration or expiration although the lung area of interest moves slightly over time with the cranio-caudal respiratory motion of the lung. This may explain the occasional, counterintuitive observation in our series as well as in others,[2] that ventral lung regions actually appear to become smaller again during late inspiration (compare Fig. 3B and C), or that density in ventral regions decreases during expiration. Such effects could be caused by respiratory motion of the (preferentially ventilated) subcardial accessory lobe of the pig lung. Deviation from a two-compartmental behaviour, i.e. existence of a third compartment, is another possibility yet to be studied. In the near future, multislice CT scanners will allow simultaneous acquisition of several slices. These image series, acquired at different cranio-caudal levels, may also allow dynamic lung volume changes to be calculated during ventilation.

The temporal resolution of the CT scanner was limited to 250 ms in this study. This resolution allows 6 data points to be obtained during 1.5 s; for example, a τ of 0.5 s is the minimum to be determined by least-squares fitting. Scanning at even better temporal resolution would be necessary if τ <0.5 s are expected. Fast dynamic CT acquisitions with an effective temporal resolution up to 100 ms are already available, and further improvement may come soon. An even better temporal resolution of about 50 ms is already obtainable by electron beam scanners (EBCT),[14] but this technology is not widely available for clinical use, and causes increased radiation exposure compared with spiral CT scanners.[15]

Even dynamic CT uses a lot of radiation. Although dosimetry was not performed in this study, preliminary data on humans show a dose of 47 mGy for a 10 s dynamic CT measurement, using the same scanner and similar acquisition parameters,[16] compared with a dose of approximately 30–40 mGy when undergoing a spiral CT of the thorax.

Clinical consequences

Different respiratory time constants and their individual contributions to lung ventilation and alveolar recruitment can be found by dynamic CT acquisition using clinical spiral CT scanners. Such analyses may help to rapidly and individually optimize ventilator settings in ARDS patients, avoid cyclic alveolar collapse and reopening, maximize ventilated lung, and reduce respirator-induced lung injury. Dynamic CT techniques open a new diagnostic field, providing a regional analysis of lung function with correlation to the underlying pathology. Further studies are necessary to establish the clinical value of this method.

Acknowledgements

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Evolution of cerebral ischaemia induced by thromboembolism in rats detected by early sequential MR imaging

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Thromboembolic stroke appears to evolve in patients in a very complicated manner. The present study investigated the evolution of thromboembolic stroke in rats (*n*=9) using a 4.7-T MR imager. Under isoflurane anaesthesia, the rats received homologous blood clots into the right internal carotid artery. After thromboembolic stroke, lesion volume, which was defined and calculated, based on apparent diffusion coefficient maps, tended to increase gradually over the 6 h magnetic resonance imaging study. The largest percentage change in lesion volume was found at the early stage (40–100 min) of thromboembolism, and showed significant correlation with total percentage change in lesion volume (41.6 (SD 32.8%)) (r=0.77, P<0.05). In conclusion, marked enlargement or diminution of lesion volume may be observed at the early stage of thromboembolism. Thromboembolic stroke, which can be partly salvaged at the early stage, may likely evolve to a lesser extent thereafter.

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Perioperative stroke is uncommon, occurring in 0.08–0.2% of general surgery patients.[1 2] Patients who undergo cardiac, neurologic, and vascular procedures have a higher perioperative stroke rate of 2.2–5.2%.[3–5] Although these events are uncommon, perioperative stroke can be associated with a mortality rate of up to 26%.[2]

Cerebral ischaemia induced by thromboembolism remains a crucial problem during the perioperative period. It may occur silently under general anaesthesia, and may cause prolonged unconsciousness, coma, or death as a result of neurological damage. One of the first steps in an attempt to prevent or attenuate this neurological damage in patients, especially those with risk factors for thromboembolism (i.e. a previous history of transient ischaemic attack, heart disease, peripheral vascular disease),[6] is to evaluate the effects on thromboembolism of neuroprotective agents or anaesthetic agents that provide some neuroprotection. However, how thromboembolic stroke evolves in humans and animals is not fully understood.

Thromboembolic stroke in patients appears to evolve in a very complicated manner. One study of patients who had suffered an acute ischaemic stroke has shown that an increase in ischaemic lesion volume occurs during the first 53 h after the stroke.[7] In 12 of these 28 patients, the initial lesion volume increased by 20% or more.[7] On the other hand, arterial cerebral occlusion leading to acute ischaemic stroke may disappear as a natural process of thrombus disintegration and endogenous thrombolysis. Jorgensen and colleagues reported that the incidence of spontaneous reperfusion was 77% in patients with cortical infarcts.[8] To determine the evolution of thromboembolic stroke, animal experiments involving sequential measurement of ischaemic lesion volume with relatively short intervals appear necessary. However, conventional structural imaging modalities (computed tomography, T_1- or T_2-weighted magnetic resonance imaging (MRI)) do not reliably depict evolving ischaemic lesions at the early stage of stroke.

Diffusion-weighted imaging (DWI) is a relatively new MRI technique that is sensitive to the microscopic motion of water molecules. The signal intensity in ischaemic brain regions on DWI appears high because the diffusion coefficient of water is reduced, presumably because of the formation of cytotoxic oedema.[9 10] This phenomenon can be quantified by the calculation of apparent diffusion coefficient (ADC) images.[11 12] The ADC may be calculated on a pixel-by-pixel basis from at least two DWIs with different

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diffusion weightings. This raises the possibility that the extent and spatial evolution of thromboembolic stroke can be evaluated using an ADC map.

The rat model of cerebral infarction was established by Kudo and colleagues.[13] This animal model of thromboembolism creates cerebral infarction predominantly in the territory of the middle cerebral artery, with a low mortality rate and excellent reproducibility.[13] To establish a remote-controlled rat thromboembolic stroke from outside the magnet, we have modified this model and observed sequential changes in the hemispheric ischaemic lesion area caused by thromboembolism.

The objective of the present study was to determine the evolution of thromboembolic stroke in rats under general anaesthesia using ADC maps. We focused on the effect of the change in lesion volume at the early stage of stroke on total evolution of thromboembolic stroke, because recent therapy in acute stroke is based on reperfusion of the ischaemic legion leading to salvage of the ischaemic penumbra, smaller infarct size, and improved outcome.[14 15]

Methods

This project was approved by, and followed the guidelines published by, the Animal Care and Use Committee of Tokyo Medical and Dental University.

Clot formation

Nine adult male Sprague–Dawley rats weighing between 330 and 400 g were used. Anaesthesia was induced with 4% isoflurane in a Plexiglas chamber. The concentration of isoflurane was then reduced to 1.5%, 1% lidocaine was locally injected for analgesia, and 0.25 ml of blood drawn from a left femoral vein and stored at room temperature for 48 h for clot formation. The clot was fragmented by extruding it twice through a 27-gauge needle. The clot fragments were then diluted with saline solution to 0.3 ml and prepared for injection.

Animal preparation

The animals were again anaesthetized with 1.5% isoflurane, and 1% lidocaine was locally administered. Under an operating microscope, the bifurcation of the right common carotid artery was exposed through a midline neck incision. The external carotid artery was ligated just above its origin. A polyethylene catheter (PE-50) was then introduced into the right common carotid artery and advanced into the internal carotid artery. Two PE-50 catheters were introduced into a right femoral vein and a right femoral artery for drug infusion, arterial pressure monitoring, and arterial blood sampling, respectively. Physiologic saline solution at 4 ml kg^{-1} h^{-1} was administered i.v. throughout the study. After a tracheostomy, each rat was ventilated with 40% oxygen and the respiratory rate controlled to maintain Pa_{CO_2} at approximately 40 mm Hg.

MRI

MRI was performed using a 4.7-T experimental imager/spectrometer system (Unity INOVA, Varian, Palo Alto, CA, USA) with a 330-mm horizontal bore magnet equipped with shielded gradients (maximal strength, 65 mT m^{-1}) and an 80-mm-ID quadrature detection coil. The slice plane was standardized by first obtaining preview spin-echo images. Spin-echo DWI (TR ms/TE ms=2000/64, 40-mm field of view, 128×128 matrix, 2-mm section thickness) consisted of nine coronal slices covering most of the rat brain. Diffusion weighting was applied along all three axes (b=0 and 1100 s mm^{-2}) and a single DWI required an acquisition time of approximately 18 min. DWI with a b value of 0 s mm^{-2} corresponds to a T_2-weighted image (T2WI).

Pairs of DWIs with two b values were used to generate maps of the ADC. ADC maps were calculated using the standard equation:[16]

$$\mathrm{ADC}=\ln(S_0/S_1)/(b_1-b_0)$$

where S_0 and S_1 are the signals of the two DWI scans and b_0 and b_1 are 0 and 1100 s mm^{-2}.

Experimental protocol

After placing the animals supine in the probe, anaesthesia was maintained with 1.5% isoflurane in 40% oxygen. The rat's body temperature was monitored with a rectal probe, and maintained at 37.5±0.5°C using a water-circulating heating pad during the MRI study. After animal positioning and shimming, a set of baseline DWIs was acquired. Homologous blood clots were introduced into the right internal carotid artery via the catheter. Sets of DWIs were acquired at 60-min intervals for 300 min beginning 40 min after clot injection (T_{40}, T_{100}, T_{160}, T_{220}, T_{280}, T_{340}). Arterial blood samples were collected at baseline, and at T_{120} and T_{240}, and analysed on a laboratory blood gas analyser (STAT profile 5™ gas analyzer, NOVA Biomedical, USA). If mean arterial pressure (MAP) was reduced to less than 80 mm Hg, dopamine was administered i.v. to maintain the MAP over 80 mm Hg.

Definition of lesion volume

The ischaemic lesion was defined arbitrarily as the pixels in which the ADC decreased to less than 70% of the mean ADC of the ipsilateral hemisphere at baseline. Lesion area on an ADC map was calculated by multiplying the number of these pixels by the area of one pixel (approximately 0.1 mm^2). The lesion volume of ischaemic injury was determined by integration of the lesion areas for the nine slices. Two coronal slices which included the optic chiasm (slice A) and the area 4 mm caudal to it (slice B) were considered to represent the territory of the middle cerebral artery, and consequently the ischaemic lesion on slices A and B were divided by the hemispheric area to obtain the percentage lesion area, and results then compared with histopathology as described below. Sequential changes in the lesion volume on ADC maps were recorded.

Percentage change in the lesion volume (%ΔLV) was defined as the percentage difference between the lesion volumes at T_t and T_{t+60} (t=40, 100, 160, 220, 280) to calculate the percentage increase or decrease during each MRI acquisition interval. The absolute values of %ΔLV were compared at different times to evaluate when the lesion volume changed (increased or decreased) markedly. Total percentage change in lesion volume (total %ΔLV) was defined to calculate percentage increase or decrease in lesion volume during the whole MRI study after thromboembolism. %ΔLV and total %ΔLV were defined and calculated as follows.

1. As DWIs were acquired at 60-min intervals, the %ΔLV between T_t and T_{t+60} was defined as: %ΔLV ($T_{t\ -\ t+60}$) (%) = [[lesion volume (T_{t+60}) − lesion volume (T_t)]/ lesion volume (T_t)]×100.
2. Total %ΔLV was calculated as: Total %ΔLV (%) = [[lesion volume (T_{340}) − lesion volume (T_{40})]/lesion volume (T_{40})]×100.

Development of lesion area in specific regions

To analyse the development of an ischaemic lesion in some specific regions, cortex and caudate putamen on slice A and cortex and basal ganglia on slice B were selected. Then the lesion in these regions was subdivided into two parts according to their ADC values: severe lesion corresponds to ADC<400×10^{-6} mm^2 s^{-1} and moderate lesion corresponds to the ischaemic lesion whose ADC value is equal to or more than 400×10^{-6} mm^2 s^{-1} but less than 500×10^{-6} mm^2 s^{-1}. Sequential changes in lesion area were recorded and analysed.

Histopathology

After MRI studies, the animals were killed with an overdose of i.v. pentobarbital, and the brain was removed and sectioned coronally at 2-mm intervals. The sections most closely corresponding to slices A and B were selected and stained with a 2% solution of triphenyltetrazolium chloride (TTC) to identify infarcted tissue, and then photographed. Using a computer imaging system, the infarcted areas were divided by the ipsilateral hemispheric area to obtain the percentage hemispheric infarcted area.

Data analysis

All data are expressed as mean (SD). MAP, arterial blood gas data, plasma glucose concentration, rectal temperature, lesion volume (area) on ADC maps, and the absolute value of %ΔLV at different times were analysed using repeated measures analysis of variance followed by Tukeys multiple comparison test. The relationship between %ΔLV during each MRI acquisition interval and the total %ΔLV was analysed using linear fitting. The relationship between lesion volume on the ADC map and the time after clot injection was analysed for each rat using linear fitting. The percentage lesion area based on the ADC map at T_{340} was compared with the TTC stained percentage hemispheric infarcted area using correlation analysis for slices A and B. Statistical significance was set at the $P<0.05$ level.

Results

No significant differences in MAP, heart rate, arterial blood gas, plasma glucose concentration, or rectal temperature at different time points throughout the study were observed (Table 1). Dopamine infusion was required in one rat to maintain MAP over 80 mm Hg.

ADC maps, DWIs, and T2WIs on slices A and B before and after thromboembolism in a representative rat are shown in Figures 1 and 2, respectively. DWI revealed a region of increased signal intensity in the territories of the right middle cerebral artery in all rats after clot injection. A clear reduction in the ADC value was evident in these regions after embolization. Lesion area was not evident on T2WI at T_{100} but apparent at T_{220} in both slices.

Mean lesion volumes did not differ significantly at the various time points. Lesion volume in individual rats showed some fluctuation during the MRI study (Figure 3). Lesion volume on the ADC map was larger at T_{340} than at T_{40} in eight of nine rats. There was a significant linear

Table 1 Haemodynamic indices, arterial blood gas, plasma glucose concentration, and rectal temperature at baseline, 100, 220, and 340 min after clot injection. Results are mean (SD). There were no significant differences in any index between any time points. MAP=mean arterial pressure; HR=heart rate

	Baseline	**100 min**	**220 min**	**340 min**
MAP (mm Hg)	113 (8)	103 (18)	97 (20)	91 (18)
HR (beats min^{-1})	329 (31)	363 (49)	393 (44)	361 (44)
Pa_{O_2} (mm Hg)	198 (23)	191 (28)	188 (29)	
Pa_{CO_2} (mm Hg)	40.2 (5.8)	37.8 (3.9)	40.1 (4.6)	
pH	7.39 (0.05)	7.38 (0.04)	7.36 (0.04)	
Plasma glucose (mg dl^{-1})	207 (38)	161 (47)	176 (51)	
Rectal temperature (°C)	37.5 (0.3)	37.6 (0.1)	37.6 (0.3)	37.6 (0.2)

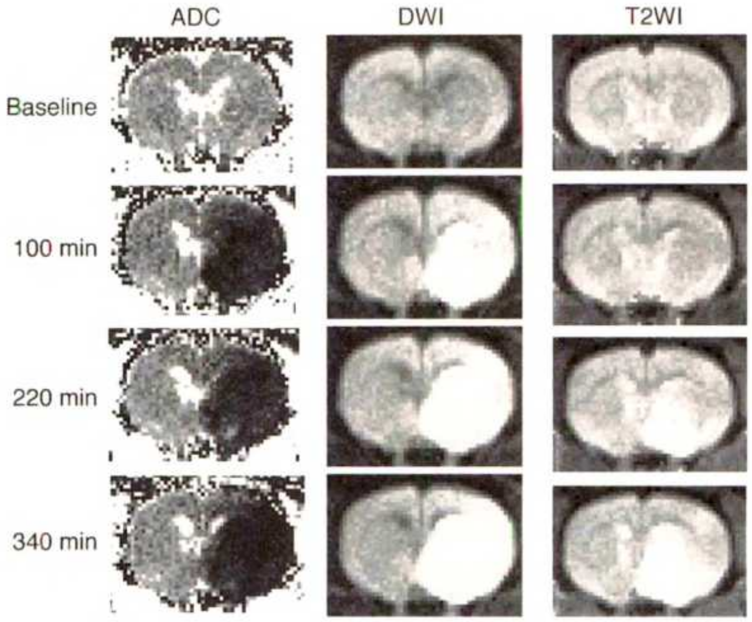

Fig 1 ADC maps, diffusion- and T_2-weighted images (DWI and T2WI) on slice A at baseline and 100, 220, and 340 min after thromboembolism.

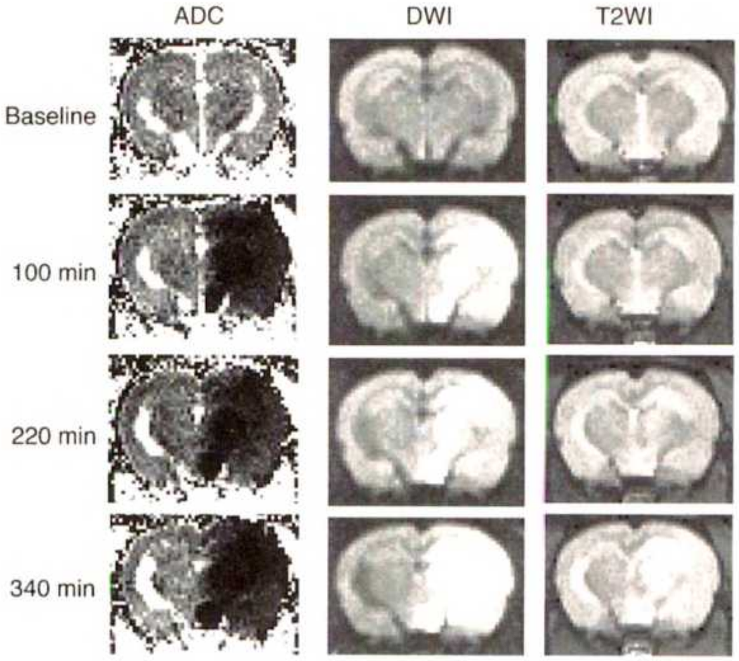

Fig 2 ADC maps, diffusion- and T_2-weighted images (DWI and T2WI) on slice B at baseline and 100, 220, and 340 min after thromboembolism.

relationship between lesion volume and the time after thromboembolism in five rats, and the mean (SD) slope and intercept were 0.43 (0.31) mm^3 min^{-1} and 243.9 (96.1) mm^3, respectively.

%ΔLV during each MRI acquisition interval is shown in Figure 4. The absolute value of %ΔLV (T_{40-100}) (22.7 (17.2)%) was two to three times larger than that at $T_{100-160}$, $T_{160-220}$, $T_{220-280}$, and $T_{280-340}$. It was significantly larger ($P<0.05$) than that at $T_{160-220}$ (7.9 (7.2)%) and $T_{280-340}$ (8.1 (8.5)%). Mean (SD) total %ΔLV was 41.6 (32.8)%. Correlation analysis revealed a significant linear correlation between %ΔLV (T_{40-100}) and total %ΔLV ($r=0.77$, $P<0.05$) (Figure 5). No significant correlation was observed between %ΔLV at other time intervals and total %ΔLV.

Severe ischaemic lesions (ADC$<400\times10^{-6}$ mm^2 s^{-1}) significantly increased with time in the cortex on both slices. In the caudate putamen on slice A and basal ganglia on slice B, mean severe ischaemic lesions doubled during MRI

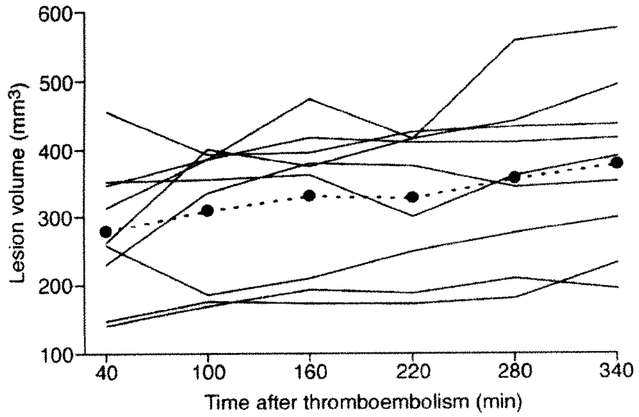

Fig 3 Sequential change in lesion volume. Mean lesion volumes (dashed line) did not differ significantly at the various time points. The lesion volume in individual rats showed some fluctuation during the MRI study (thick lines).

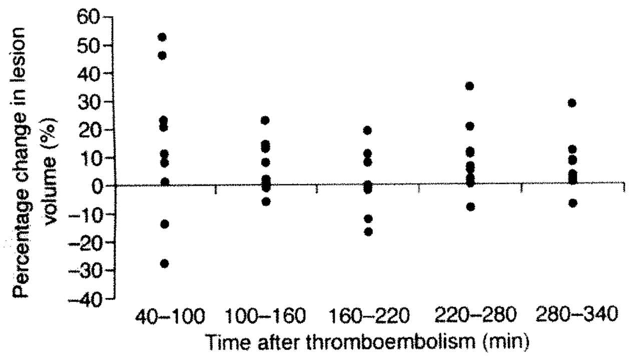

Fig 4 Percentage change in lesion volume (%ΔLV) at each MRI acquisition interval. The absolute value of %ΔLV at 40–100 min after thomboembolism was two or three times larger than at other intervals.

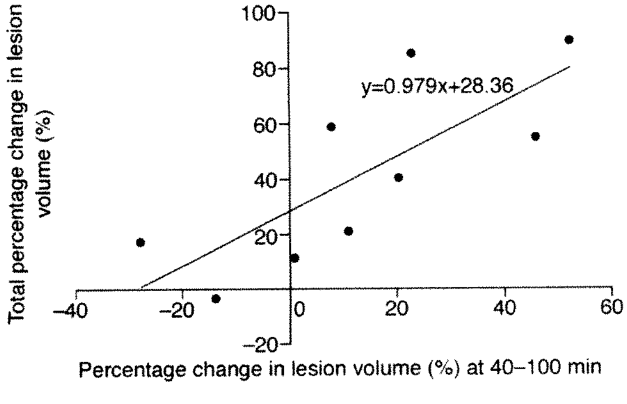

Fig 5 Correlation analysis between percentage change in lesion volume at 40–100 min after thromboembolism (%ΔLV (T_{40-100})) and total percentage change in lesion volume (total %ΔLV). There was a significant relationship (r=0.77, P<0.05).

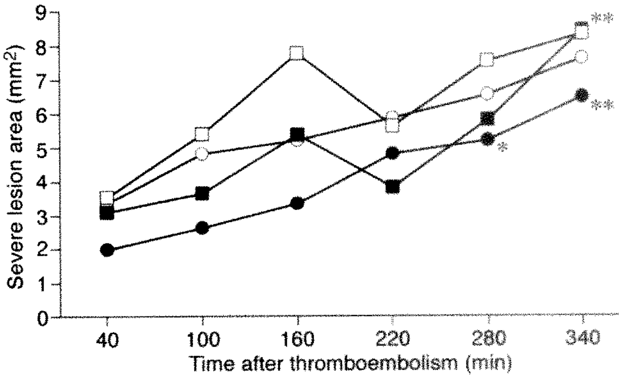

Fig 6 Sequential changes in mean severe ischaemic lesions in the cortex (●), and caudate putamen (○) on slice A and cortex (■) and basal ganglia (□) on slice B. Severe ischaemic lesions significantly increased with time in the cortex on both slices. SD are not shown for clarity. *P<0.05, **P<0.01 *vs* 40 min.

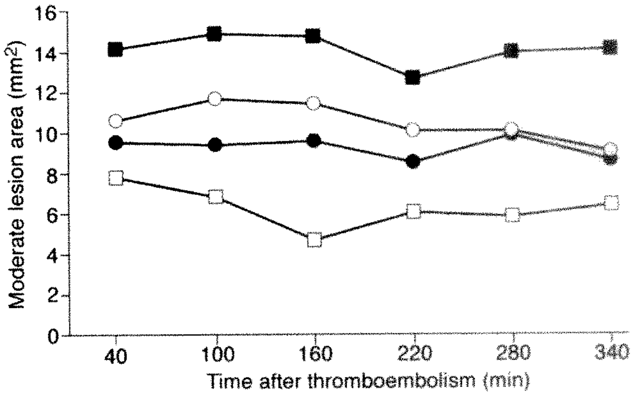

Fig 7 Sequential changes in mean moderate ischaemic lesions in the cortex (●), and caudate putamen (○) on slice A and cortex (■) and basal ganglia (□) on slice B. There was no significant differences in moderate ischaemic lesions at different time points in any selected region. SD are not shown for clarity.

study, but there was no significant differences at the various time points (Figure 6). There was also no significant differences in moderate ischaemic lesions (400×10^{-6} mm^2 s^{-1}≤ADC<500×10^{-6} mm^2 s^{-1}) at different time points in any selected region (Figure 7).

Mean (SD) percentage hemispheric infarcted area determined by TTC was 62.9 (17.8) and 56.8 (17.2)% on slices A and B, respectively. Postmortem TTC studies showed that all the animals had an infarction that correlated well to the hyperintense area on DWI and the area with a low ADC value on the ADC map. Significant correlation between the percentage hemispheric infarcted area and the hemispheric lesion area on the final ADC map for slices A and B was observed (Figure 8).

Discussion

We have assessed the evolution of thromboembolic stroke in rats using ADC maps. The lesion area was defined based on ADC maps for nine coronal slices and integrated to calculate lesion volume. Mean lesion volume tended to

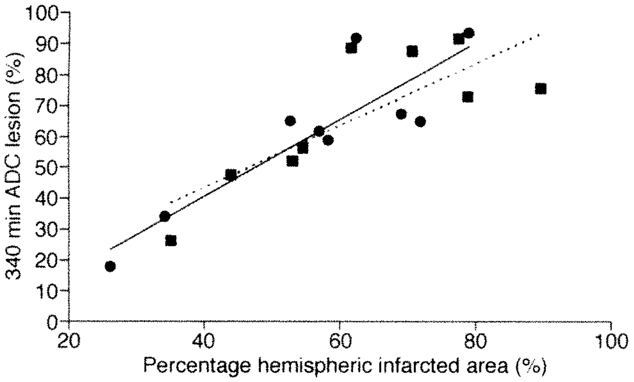

Fig 8 Percentage hemispheric infarcted area (%, *x*) and percentage lesion area on ADC map at 340 min after thromboembolism (%, *y*). There was a significant correlation on slices A (●, solid line) and B (■, dashed line). (A) $y=1.23x + 8.57$ ($r=0.88$, $P<0.01$). (B) $y=1.00x + 3.33$ ($r=0.80$, $P<0.01$).

increase with time although there was no significant difference at various time points and in individual rats there was some fluctuation. Lesion volume showed a maximal change at T_{40-100}, and a significant correlation was observed between the percentage change in lesion volume during that period (%ΔLV (T_{40-100})) and the total change in lesion volume (total %ΔLV).

Diffusion-weighted MR imaging has been well established as a reliable non-invasive method for early detection of cerebral ischaemic stroke.[17 18] The principle of diffusion measurement is that the spatial location of each water molecule is tagged such that any net movement of the water molecule over time results in a signal loss or darkening of the images. In the present study, this tagging was achieved by a pair of very strong pulsed magnetic field gradients (diffusion gradients) which were added to a spin-echo sequence. The first of these diffusion gradients causes the spinning protons to fall out of phase with one another, and the second gradient rephases the protons completely with one another only if there has been no movement of the water molecules between the application of the two diffusion gradients. When there is movement of water, the protons are not brought back completely into phase by the second diffusion gradient and the signal attenuation will occur on DWIs. DWI can detect abnormalities within min after the onset of ischaemia in animal models of stroke.[19–21] before lesions are apparent on conventional images. The high signal intensity on the DWIs after clot injection may be explained as an ischaemic change as a result of thromboembolism. The infarct lesions revealed by TTC staining may also suggest that the hyperintense areas on DWIs are ischaemic because of decreased blood flow, which is consistent with the histopathological findings of Kudo and colleagues.[13]

After injection of the clot, the ADC values were reduced in regions where the signal intensities were increased on the DWIs. Although the precise mechanism underlying the reduction in ADCs in ischaemic regions is unclear, this phenomenon is considered to represent the onset of intracellular water accumulation or cytotoxic oedema.[10 22 23] Tissue adenosine triphosphate (ATP) reserves are depleted after the onset of ischaemia, and the subsequent failure of the Na^+/K^+-ATPase pump causes water protons and ions to migrate from the faster-diffusing, extracellular space into the slower-diffusing, more restricted intracellular compartment, resulting in an ADC decrease.

Thromboembolic stroke in patients evolves in a very complicated manner. For example, the ischaemic lesion may enlarge with time[7] and result in large cerebral infarction. On the other hand, spontaneous reperfusion may occur[8] and ischaemic penumbra may be salvaged. Many studies have shown a qualitative enlargement of thromboembolic stroke in rats but not quantitative changes in lesion volume in individual rats.[24–29] Thus, we designed the present study to examine how lesion volume after thromboembolism evolves quantitatively using ADC maps. Lesion volumes were measured sequentially at relatively short intervals (60 min). The precise mechanisms responsible for the change in lesion volume after thromboembolism are not fully understood. We assume many factors are involved, as described below.

First, mean percentage lesion volume tended to increase with time after thromboembolism in the present study; however, the increase was not statistically significant. This enlargement of lesion volume may be most likely explained by an ischaemic penumbra. The lesion observed on the first ADC map after the thromboembolic stroke may be regarded as the central most severely ischaemic region ('core'[30]). The lesion area that was not visible on the ADC map on the early stage of the thromboembolism but was detected later during the MRI study may represent 'penumbra'.[30 31] Although cerebral perfusion was not evaluated in the present study, the most likely scenario is that cerebral blood flow in the 'penumbra' reduced slightly and the ADC decreased little or did not change[32] on the first ADC map after thromboembolism. This hypoperfused tissue may be above the threshold for infarction, at least initially;[33] however, it may be irreversibly injured on the time course of the MRI study.

Development of severe ischaemic lesions in the cortex on slices A and B may support our assumption that the enlargement of lesion volume may be most likely explained by an ischaemic penumbra. The increase in severe ischaemic lesion area may be explained that the regions with higher ADC value ($\geqslant 400 \times 10^{-6}$ mm^2 s^{-1}) became injured during the time course of the experiment. The area of moderate lesion was unchanged because the higher ADC regions ($\geqslant 500 \times 10^{-6}$ mm^2 s^{-1}) may have been injured and showed a decrease in their ADC value to 400–500$\times 10^{-6}$ mm^2 s^{-1}.

Second, as shown in Figure 3, the lesion volume in individual rats showed some fluctuation during the MRI study. Transient reduction in lesion volume (transient recoveries of ADCs) in such animals may be, in part, explained by recanalization and subsequent reperfusion (spontaneous reperfusion[8,34]), a passage of emboli or a development of adequate collateral circulation. Disappearance of arterial cerebral occlusion is often seen clinically as a natural process of thrombus disintegration and endogenous thrombolysis. Although it is impossible to prove in the present study without measurement of cerebral perfusion, the proportional relationship between ADC and cerebral perfusion[32] may indirectly support our assumption.

Third, pseudonormalization of the ADC may be another factor that affected the time course of lesion volume. In rodent stroke models, ADC begins to normalize at 24–48 h. This normalization does not imply tissue recovery but the beginning of tissue necrosis (pseudonormalization).[35,36] As ADC is increased by vasogenic oedema,[22] pseudonormalization is considered to be attributed to a balance of cytotoxic and vasogenic oedema. Lesion area was evident on T2WI at T_{220} in the present study, suggesting that vasogenic oedema occurred at that time. Lesion volume based on ADC maps may have been affected by pseudonormalization of ADC during the latter half of the time course of the MRI study; however, we assume the extent of underestimation of lesion volume because of pseudonormalization, if it occurred, may be small as the TTC stained infarcted area correlated well with lesion volume on the final ADC map.

The fact that the absolute value of $\%\Delta LV$ was largest at T_{40-100} may imply that lesion volume markedly increases or decreases at the early stage of thromboembolism. Irrespective of the mechanisms responsible for the sequential change observed in lesion volume, our data demonstrate that total $\%\Delta LV$ shows significant correlation to $\%\Delta LV$ at this period (T_{40-100}) but not thereafter. This suggests that enlargement or diminution of lesion volume during this period plays an important role in the total evolution of thromboembolic stroke in this model. Our results also suggest that only a small increase or even a decrease in lesion volume may be detected throughout the whole period of thromboembolism in rats in which the ischaemic lesion is partly salvaged at the early stage of thromboembolic stroke.

There is no absolute threshold of ADC decrease that predicts if a lesion is irreversible; maximal decreases in the ADC area are even reversible for short periods.[37] This is why the threshold ADC values should be set arbitrarily. The mean (SD) ADC value on slices A and B at baseline were 718 (40)$\times10^{-6}$ and 703 (44)$\times10^{-6}$ mm^2 s^{-1}, respectively. We have set the threshold at 70% of the baseline, which corresponded to approximately 500×10^{-6} mm^2 s^{-1}, by modifying the study by Busch and colleagues.[38] Morikawa and colleagues reported on the adverse effect of hyperglycaemia on transient focal brain ischaemia using the threshold ADC value of 500×10^{-6} mm^2 s^{-1}.[39] One may expect that −2 SD from the mean ADC at baseline would be better as the threshold ADC. The mean −2 SD ADC on slices A and B correspond to 583×10^{-6} and 539×10^{-6} mm^2 s^{-1}, respectively in the present study, which would have estimated the lesion volume (area) a little larger than our analysis.

In conclusion, the largest percentage change in lesion volume was found at the early stage of thromboembolism, and showed significant correlation with the total percentage change in lesion volume. Marked enlargement or diminution of the lesion volume may be observed at the early stage of thromboembolism. Thromboembolic stroke, which is partly salvaged at the early stage, may likely evolve to a lesser extent thereafter.

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REVIEW ARTICLE

Tetanus: a review of the literature

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Tetanus is now a rare disease in the developed world. However, it remains an important cause of death worldwide and is associated with a high case mortality, particularly in the developing world. There are an estimated 800 000–1000 000 deaths from tetanus each year.[28] Although the incidence in developed countries is low, the mortality in the group most at risk of contracting the illness, patients over 60 yr, remains above 50%.[78] Modern intensive care management should prevent death from acute respiratory failure,[109] but cardiovascular complications as a result of autonomic instability and other causes of death remain problematic. In this article, we review the epidemiology, pathophysiology, clinical features, and current management of tetanus.

Epidemiology

In spite of the World Health Organization's intention to eradicate tetanus by the year 1995, it remains endemic in the developing world and WHO estimated approximately 1000 000 deaths from tetanus worldwide in 1992. This included 580 000 deaths from neonatal tetanus, with 210 000 in South East Asia and 152 000 in Africa.[43] The disease is uncommon in developed countries. In South Africa approximately 300 cases occur each year,[118] approximately 12–15 cases are reported each year in Britain[43] and between 50 and 70 in the USA.[45]

Microbiology

Tetanus is caused by a Gram-positive bacillus, *Clostridium tetani*. This is a ubiquitous bacterium with a natural habitat of soil, but can also be isolated from stools of domestic animals and humans.[118] It is a motile, spore-forming obligate anaerobe. The spore is incompletely destroyed by boiling but eliminated by autoclaving at 1 atmosphere pressure and 120°C for 15 min. It is rarely cultured, as the diagnosis of the disease is clinical. *Clostridium tetani* produces its clinical effects via a powerful exotoxin. The role of the toxin within the organism is not known.[75] The DNA for this toxin is contained in a plasmid. Presence of the bacterium does not indicate infection, as not all strains possess the plasmid. Bacterial antimicrobial sensitivity has been little investigated.

Vaccination

As the organism is ubiquitous and infection does not confer immunity, prevention is through vaccination. Tetanus vaccine has been available since 1923. Routine vaccination began in the UK in 1961.[56] Vaccination is started at 2 months of age with three injections performed at monthly intervals.[56] The second injection confers immunity[96] with the third prolonging its duration.[103] A booster is given before the age of 5 yr.[56] Similar responses occur in older children and adults.[80] Neonatal immunity is provided by maternal vaccination and transplacental transfer of immunoglobulin. This may be impaired in the presence of maternal HIV infection.[27] Immunity is not lifelong. Revaccination at 10-yr intervals is recommended in the USA.[44] In the UK, two boosters spaced 10 yr apart are recommended in adulthood, so the recommendations do not extend to vaccination beyond the third decade.[56]

In the USA, more than 70% of cases[78] and 80% of deaths[45] occur in those over 50 yr. Similar proportions are reported in Europe.[89] In the UK and USA, serological surveys have demonstrated an increasing proportion of patients with inadequate immunity as age increases: 49–66% of patients over 60 yr had antibody levels below the protective level[22 45 91 97 115] Some have never been vaccinated, while others have lost their immunity.[89]

Pathophysiology

Under anaerobic conditions found in necrotic or infected tissue, the tetanus bacillus secretes two toxins: tetanospas-

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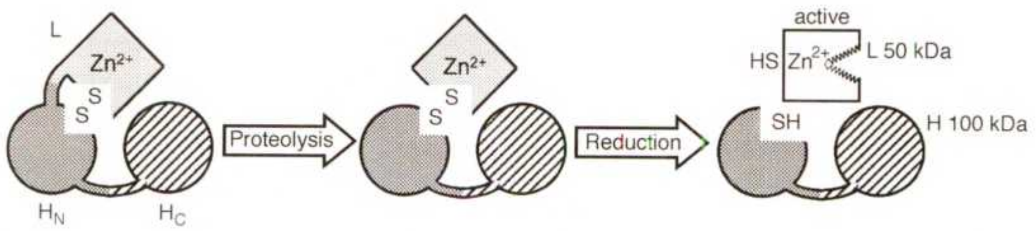
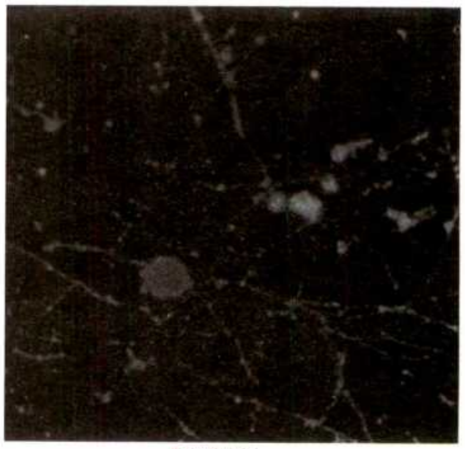


Fig 1 Scheme of the structure and mechanism of activation of tetanus and botulinum neurotoxins. The toxins are produced as an inactive single polypeptide chain of 150 kDa, composed of three 50 kDa domains, connected by protease-sensitive loops. The toxins are activated upon selective proteolytic cleavage, which generates two disulphide-linked chains: L (50 kDa) and H (100 kDa). The three domains play different functional roles in cell penetration: H_c is responsible for cell binding and H_n for cell penetration. Reduction takes place inside the nerve cells and liberates the activity of the L chain in the cytosol. L is a zinc-endopeptidase specific for protein components of the neuroexcytosis apparatus. Originally published in *Quarterly Review of Biophysics* 1995.[76]

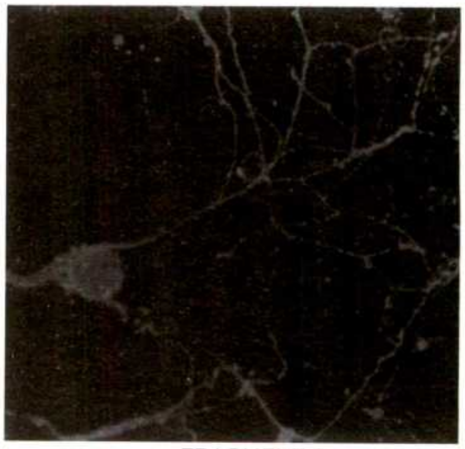
min and tetanolysin. Tetanolysin is capable of locally damaging otherwise viable tissue surrounding the infection and optimizing the conditions for bacterial multiplication.[87]

Tetanospasmin leads to the clinical syndrome of tetanus. This toxin may constitute more than 5% of the weight of the organism.[74] It is a two-chain polypeptide of 150 000 Da which is initially inactive. The heavy chain (100 000 Da) and the light chain (50 000 Da) are linked by a protease sensitive loop that is cleaved by tissue proteases leaving a disulphide bridge linking the two chains. The carboxyl terminus of the heavy chain binds to neural membrane and the amino terminus facilitates cell entry.[120] The light chain acts pre-synaptically to prevent neurotransmitter release from affected neurones. Released tetanospasmin spreads to underlying tissue and binds to gangliosides GD_{1b} and GT_{1b} on the membranes of local nerve terminals. If toxin load is high, some may enter the bloodstream from where it diffuses to bind to nerve terminals throughout the body. The toxin is then internalized and transported intra-axonally and retrogradely[39] to the cell body.[65] Transport occurs first in motor[9] and later in sensory and autonomic nerves (Fig. 2).[116] Once in the cell body the toxin can diffuse out so affecting and entering nearby neurones. When spinal inhibitory interneurones are affected symptoms occur.[11] Further retrograde intraneural transport occurs with toxin spreading to the brainstem and midbrain. This passage includes retrograde transfer across synaptic clefts by a mechanism that is unclear.

After internalization into inhibitory neurones the disulphide bonds linking the light and heavy chains are reduced, liberating the light chain. The effects of the toxin result from prevention of the release of neurotransmitters.[21 23 24] Synaptobrevin is a membrane protein necessary for the export of intracellular vesicles containing neurotransmitter. The tetanospasmin light chain is a zinc metalloprotease, which cleaves synaptobrevin at a single point, thereby preventing neurotransmitter release.[84 100] The toxin has a predominant effect on inhibitory neurones, inhibiting release of glycine and gamma-aminobutyric acid (GABA).[21 23 24] Interneurones inhibiting alpha motor neurones are first affected and the motor neurones lose inhibitory control. Later (because of the longer path) preganglionic sympathetic neurones in the lateral horns and the parasympathetic centres are also affected. Motor neurones are similarly affected and the release of acetylcholine into the neuromuscular cleft is reduced.[11] This effect is similar to the action of the closely related botulinum toxin, which produces a flaccid paralysis.[75] However, in tetanus the



$MBP\text{-}TC_{271\text{-}451}$



FRAGMENT C

Fig 2 Radio-labelled fragment C of tetanus toxin in the dorsal root ganglion showing tetanus toxin within axons and nerve cell bodies. (Kindly provided by Dr N. Fairweather of Department of Biochemistry, Imperial College, London.)

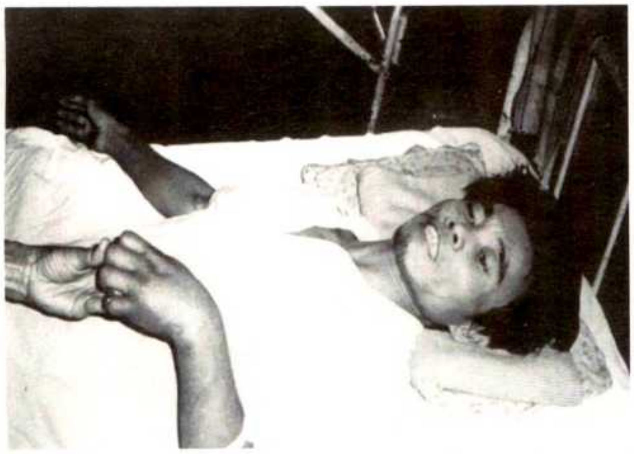


Fig 3 Risus sardonicus. (Kindly provided by Dr J. Farrar and Dr C. Parry of the University of Oxford Clinical Research Unit, Centre for Tropical Diseases, Ho Chi Minh City, Viet Nam.)

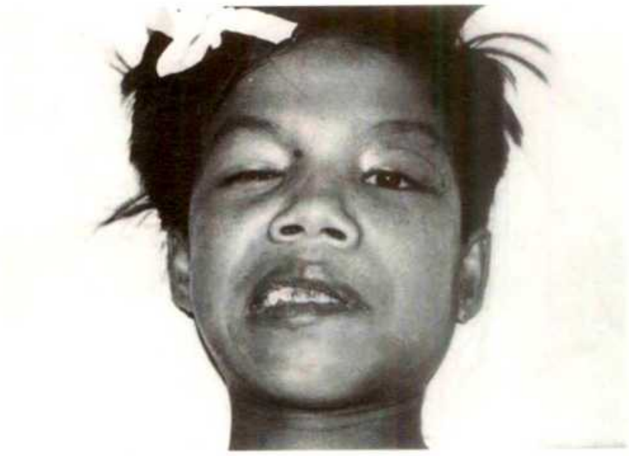


Fig 4 Left facial nerve palsy and recent scar in patient with cephalic tetanus. (Kindly provided by Dr T. M. Cook, taken at the University of Oxford Clinical Research Unit, Centre for Tropical Diseases, Ho Chi Minh City, Viet Nam.)

disinhibitory effect on the motor neurone overwhelms any diminution of function at the neuromuscular junction. Medullary and hypothalamic centres may also be affected. Tetanospasmin has a cortical convulsant effect in animal studies.[14 19] Whether these mechanisms contribute to intermittent spasm and autonomic storms is unclear. The prejunctional effect on the neuromuscular junction may lead to considerable weakness between spasms[75] and might account for both the paralysis of cranial nerves observed in cephalic tetanus[57] and myopathies observed after recovery.[75] In other species, tetanus produces an illness characterized by flaccid paralysis.[75]

Uncontrolled disinhibited efferent discharge from motor neurones in the cord and brainstem leads to intense muscular rigidity and spasm, which may mimic convulsions. The reflex inhibition of antagonist muscle groups is lost and agonist and antagonist muscles contract simultaneously. Muscle spasms are intensely painful and may lead to fractures and tendon rupture. Muscles of the jaw, face, and head are often involved first because of their shorter axonal pathways. The trunk and limbs follow but peripheral muscles in the hands and feet are relatively spared.

Disinhibited autonomic discharge leads to disturbances in autonomic control, with sympathetic overactivity and excessive plasma catecholamine levels.

Neuronal binding of toxin is thought to be irreversible. Recovery requires the growth of new nerve terminals[11 33 98] which explains the prolonged duration of tetanus.

Clinical features

Tetanus usually follows a recognized injury. Contamination of wounds with soil, manure, or rusty metal can lead to tetanus. It can complicate burns, ulcers, gangrene, necrotic snakebites, middle ear infections, septic abortions, childbirth, intramuscular injections, and surgery. Injuries may be trivial and in up to 50% of cases the injury occurs indoors and/or is not considered serious enough to seek medical treatment.[37 78] In 15–25% of patients, there is no evidence of a recent wound.

There is a clinical triad of rigidity, muscle spasms and, if severe, autonomic dysfunction. Neck stiffness, sore throat, and difficulty opening the mouth are often early symptoms.[4 37] Masseter spasm causes trismus or 'lockjaw'. Spasm progressively extends to the facial muscles causing the typical facial expression, 'risus sardonicus', and muscles of swallowing causing dysphagia (Fig. 3). Rigidity of the neck muscles leads to retraction of the head. Truncal rigidity may lead to opisthotonus and respiratory difficulty with decreased chest wall compliance.

In addition to increased muscle tone, there are episodic muscular spasms. These tonic contractions have a convulsion-like appearance affecting agonist and antagonist muscle groups together. They may be spontaneous or triggered by touch, visual, auditory, or emotional stimuli. Spasms may vary in severity and frequency but may be strong enough to cause fractures and tendon avulsions.[11] Spasms may be almost continual, leading to respiratory failure.[69] Pharyngeal spasms are often followed by laryngeal spasms and are associated with aspiration and life-threatening acute airway obstruction.

In the commonest form of tetanus, *generalized tetanus*, muscles throughout the body are affected. The muscles of the head and neck are usually affected first with progressive caudal spread of rigidity and spasm to affect the whole body. The differential diagnosis includes orofacial infection, dystonic drug reactions, hypocalcaemia, strychnine poisoning, and hysteria.

With lower toxin loads and peripheral injuries *local tetanus* is seen. Spasm and rigidity are restricted to a limited area of the body.[35] Mortality is greatly reduced. An exception to this is *cephalic tetanus* when localized tetanus

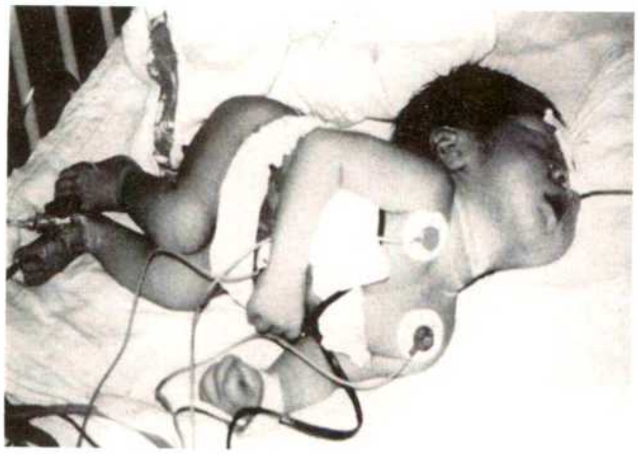


Fig 5 Severe opisthotonos in tetanus neonatorum. (Kindly provided by Dr J. Farrar and Dr C. Parry of the University of Oxford Clinical Research Unit, Centre for Tropical Diseases, Ho Chi Minh City, Viet Nam.)

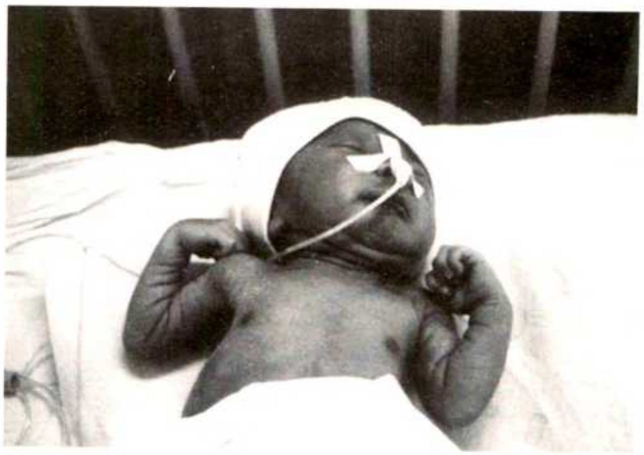


Fig 6 Severe spasm with flexion of the arms in tetanuus neonatorum. Dr J. Farrar and Dr C. Parry of the University of Oxford Clinical Research Unit, Centre for Tropical Diseases, Ho Chi Minh City, Viet Nam.

from a head wound affects the cranial nerves; paralysis rather than spasm predominates at presentation (Fig. 4), but progression to generalized tetanus is common and mortality is high.[57]

Tetanus neonatorum causes more than 50% of deaths from tetanus worldwide[43] but is very rare in developed countries.[78] Neonates present within a week of birth with a short history of failure to feed, vomiting, and 'convulsions'. Seizures, meningitis, and sepsis are differential diagnoses (Figs 5 and 6). Spasms are generalized and mortality is high. Poor umbilical hygiene is the cause of the disease but it is entirely preventable by maternal vaccination, even during pregnancy.[26]

Before the introduction of artificial ventilation, many patients with severe tetanus died from acute respiratory failure.[109] With the development of intensive care it became apparent that severe tetanus was associated with marked autonomic instability.[37 64] The sympathetic nervous system is most prominently affected. Clinically, increased sympathetic tone causes persistent tachycardia and hypertension. Marked vasoconstriction and pyrexia are seen. Basal plasma catecholamine levels are raised.[63] 'Autonomic storms' occur with marked cardiovascular instability. Severe hypertension and tachycardia may alternate with profound hypotension, bradycardia, or recurrent cardiac arrest.[64 110] These alterations are a result of, predominantly, rapid alterations in systemic vascular resistance rather than cardiac filling or performance.[58 108] During these 'storms' plasma catecholamine levels are raised up to 10-fold, to similar levels to those seen in phaeochromocytoma.[31 62 108] Norepinephrine is affected more than epinephrine.[31 108] Neuronal hyperactivity rather than adrenal medullary hyperactivity appears to predominate.[108 111]

In addition to the cardiovascular system, other autonomic effects include profuse salivation and increased bronchial secretions. Gastric stasis, ileus, diarrhoea, and high output renal failure may all be related to autonomic disturbance.

The involvement of the sympathetic nervous system is established.[64] The role of the parasympathetic system is less clear. Tetanus has been reported to induce lesions in the vagal nuclei,[8] while locally applied toxin may lead to excessive vagal activity.[5] Hypotension, bradycardia, and asystole may arise from increased vagal tone and activity.[37 111]

Natural history

The *incubation period* (time from injury to first symptom) averages 7–10 days, with a range of 1–60 days. The *onset time* (time from first symptom to first spasm) varies between 1–7 days. Shorter incubation and onset times are associated with more severe disease. The first week of the illness is characterized by muscle rigidity and spasms, which increase in severity. Autonomic disturbance usually starts several days after the spasms and persists for 1–2 weeks. Spasms reduce after 2–3 weeks, but stiffness may persist considerably longer. Recovery from the illness occurs because of regrowth of axon terminals[11 33 98] and by toxin destruction.[25]

Severity grading

Several grading systems (Phillips, Dakar, Udwadia) are reported.[86 111 113] The system reported by Ablett is most widely used (Table 1).[1]

Altered cardiovascular physiology

There have been relatively few studies of the effects of tetanus on the cardiovascular system. One problem is that the haemodynamic effects of both complications and

Table 1 Ablett classification of severity of tetanus[1]

Grade	Clinical features
I	Mild: mild to moderate trismus; general spasticity; no respiratory embarrassment, no spasms, little or no dysphagia.
II	Moderate moderate trismus; well-marked rigidity, mild to moderate but short spasms, moderate respiratory embarrassment with an increased respiratory rate greater than 30; mild dysphagia
III	Severe: severe trismus; generalized spasticity, reflex prolonged spasms, increased respiratory rate greater than 40, apnoeic spells, severe dysphagia; tachycardia greater than 120
IV	Very severe grade III and violent autonomic disturbances involving the cardiovascular system Severe hypertension and tachycardia alternating with relative hypotension and bradycardia, either of which may be persistent

treatment may mask the true effects of the disease itself. Udwadia studied 27 patients with Ablett grade III/IV disease who were stable and not on drugs likely to alter haemodynamics.[111] Nineteen had uncomplicated and eight complicated tetanus (with pneumonia, ARDS, sepsis). His extensive studies examined cardiovascular features of the disease: changes during poorly controlled spasms, during intense relaxation, during recovery, and the effect of fluid loading in tetanus compared with the effect in healthy volunteers. He also studied patients during periods of considerable cardiovascular instability because of autonomic storms.

Severe uncomplicated tetanus was marked by a hyperkinetic circulation. Tachycardia was universal with hypertension, raised stroke volume index, and raised cardiac index. Other findings were low normal systemic vascular resistance and normal left- and right-sided filling pressures. These findings were similar to those of James and Manson.[58] The hyperkinetic state was exaggerated during poor relaxation and increased spasm activity. The haemodynamic abnormalities became less marked during periods of full muscular relaxation but measurements only gradually returned to normal ranges during recovery from the disease. A fluid challenge of 2000 ml increased left heart filling pressures and cardiac index but these effects were very transient. During autonomic storms with marked cardiovascular instability, patients fluctuated from a hyperstimulated state of hypertension (arterial pressure up to 220/120 mm Hg) and tachycardia (heart rate 130–190 beats min^{-1}) to one of profound depression with hypotension (as low as 70/30 mm Hg), bradycardia (50–90 beats min^{-1}) and a fall in CVP (reducing from 6 to 1 cm H_2O). Invasive monitoring showed these changes to be a result of a rapid, marked alteration in systemic vascular resistance index (SVRI), falling from 2300 to less than 1000 dynes s cm^{-5} m^{-2}. There was little change in cardiac index or filling pressures. Patients with grade IV disease were less likely than those with less severe disease to raise cardiac index or cardiac work indices in response to fluid load or during alterations in vascular resistance seen during autonomic storms. One patient with severe sustained hypertension was found to have massively raised vascular resistance with SVRI greater than 4500 dynes s cm^{-5} m^{-2}. In complicated tetanus, measurements varied widely with no consistent findings.

The hyperkinetic circulation is largely because of increased basal sympathetic activity and muscle activity, with a lesser effect from raised core temperature. The low-normal SVRI is because of extensive vasodilation in metabolically active muscles. As oxygen extraction ratio does not alter in tetanus, the increased demand must be delivered by increased blood flow. Poor spasm control exaggerates these effects. Fluid loading causes only a transient rise in filling pressures, cardiac index, and LVSWI, because the circulation is widely vasodilated and hence is a high capacitance system in comparison to normal controls. In uncomplicated tetanus, the cardiovascular system, therefore, mimics that of the normal patient undergoing intense exercise. Grade IV patients appear less able to increase cardiac performance and, therefore, are more susceptible to profound hypotension and shock during acute vasodilatory storms. The mechanism is unclear but may relate to sudden withdrawal of catecholamine stimulation or a direct action of tetanus toxin on the myocardium. Altered myocardial function may be because of persistently raised catecholamine levels[95] but abnormal function may occur even in the absence of sepsis or high catecholamine levels.[54]

Altered respiratory physiology

Muscular rigidity and spasms of the chest wall, diaphragm, and abdomen lead to a restrictive defect. Pharyngeal and laryngeal spasms predict respiratory failure or life-threatening airway obstruction. Poor cough from rigidity, spasms, and sedation leads to atelectasis and the risk of pneumonia is high. The inability to swallow copious saliva, profuse bronchial secretions, pharyngeal spasms, raised intra-abdominal pressure, and gastric stasis all increase the risk of aspiration, which is common. Ventilation/perfusion mismatching is also common. Consequently, hypoxia is a uniform finding in moderate or severe tetanus even when the chest is radiologically clear.[112] Breathing air, oxygen tensions of between 5.3–6.7 kPa are common. In artificially ventilated patients, increased A-a gradients persist.[112] Oxygen delivery and utilization may be compromised even without super-added lung pathology. Acute respiratory distress syndrome may occur as a specific complication of tetanus.[111] Minute ventilation may be altered by a variety of causes. Hyperventilation may occur because of fear, autonomic disturbance, or alteration in brainstem function.[71]

Hypocarbia (Pco_2 4.0–4.6 kPa) is usual in mild to moderate disease.[112] Hyperventilation 'storms' may lead to severe hypocarbia (Pco_2 <3.3 kPa). In severe disease, hypoventilation from prolonged spasms and apnoea occurs.[69] Sedation, exhaustion and altered brainstem function may also lead to respiratory failure. Respiratory drive may be deficient leading to recurrent life-threatening apnoeic periods.[112]

Altered renal physiology

In mild tetanus, renal function is preserved. In severe disease reduced glomerular filtration rate and impaired renal tubular function are frequent.[101] Contributory causes of renal failure include dehydration, sepsis, rhabdomyolosis, and alterations in renal blood flow secondary to catecholamine surges. Renal failure may be oliguric or polyuric. Clinically important renal impairment is associated with autonomic instability[51] and histology is normal or shows acute tubular necrosis.[101]

Management

Treatment strategies involve three management principles: organisms present in the body should be destroyed to prevent further toxin release; toxin present in the body, outside the CNS should be neutralized; and the effects of toxin already in the CNS should be minimized.

Neutralization of unbound toxin

Human tetanus *immune globulin* 3–6000 units is given i.m.[2 4 48]

Removal of the source of infection

Where present, obvious wounds should be surgically debrided.[2 37 48] *Penicillin* has been widely used for many years but is a GABA antagonist and associated with convulsions.[61] *Metronidazole* is probably the antibiotic of choice. It is safe and comparative studies with penicillin suggest at least as good results.[3 121] Erythromycin, tetracycline, chloramphenicol, and clindamycin are all accepted as alternatives.[2 4 37 48]

Control of rigidity and spasms

Avoidance of unnecessary stimulation is mandatory, but the mainstay of treatment is sedation with a *benzodiazepine*. Benzodiazepines augment GABA agonism, by inhibiting an endogenous inhibitor at the $GABA_A$ receptor. Diazepam may be given by various routes, is cheap and widely used, but long acting metabolites (oxazepam and desmethyldiazepam) may lead to cumulation and prolonged coma. Doses as high as 100 mg h^{-1} have been reported.[72] Midazolam has been used with less apparent cumulation.[50] Additional sedation may be provided by *anticonvulsants*, particularly phenobarbitone (which further enhances GABAergic activity)[60] and *phenothiazines*, usually chlorpromazine.[25] Propofol has been used for sedation with rapid recovery on stopping the infusion.[13 83]

When sedation alone is inadequate, ***neuromuscular blocking agents*** and intermittent positive pressure ventilation may be required for a prolonged period. Traditionally, the long acting agent pancuronium has been used.[36] However, pancuronium inhibits catecholamine re-uptake and could worsen autonomic instability in severe cases. There have been isolated reports of worsening hypertension and tachycardia associated with its use.[18 40] But Dance reported no difference in complications in those treated with pancuronium compared with other neuromuscular blocking drugs.[25] Vecuronium is free from cardiovascular side-effects and histamine release but is relatively short-acting.[40 88] The use of an atracurium infusion in tetanus for 71 days has been reported.[81] In this patient, with normal renal and hepatic function, there was no cumulation of laudanosine, the epileptogenic metabolite of atracurium. Longer-acting agents are preferable as they lend themselves to administration by intermittent bolus rather than requiring infusion. Prolonged use of aminosteroid neuromuscular blocking agents (vecuronium, pancuronium, rocuronium, and pancuronium), particularly by infusion, has been associated with critical illness neuropathy and myopathy,[41] but this has not been reported in tetanus. Of the newer agents, pipecuronium and rocuronium are long acting 'clean' agents but are expensive. Individual drugs have not been compared in randomized trials.

The use of *dantrolene* to control refractory spasms has been reported in one case.[107] Neuromuscular blocking drugs were unnecessary after its administration, paroxysmal spasms stopped and the patient's condition improved.

Sedation with *propofol* has allowed control of spasms and rigidity without the use of neuromuscular blocking drugs.[13] Examination of the EMG and neuromuscular function during propofol boluses.[12] showed an 80% reduction in EMG activity without alteration of function at the neuromuscular junction. However, drug levels were closer to anaesthetic than sedative concentrations and mechanical ventilation would be required.

Intrathecal *baclofen* (a $GABA_B$ agonist) has been reported in several small series with varying success.[32 92 99] Doses ranged from 500 to 2000 µg each day, given as boluses or infusion. Larger doses and boluses were associated with more side-effects.[32] In all the reports, a significant number of patients developed coma and respiratory depression necessitating ventilation.[32 99] In some cases, adverse effects were reversible with the $GABA_A$ antagonist flumazenil, but this is not reliable.[32] The technique is invasive, costly and facilities for artificial ventilation must be immediately available.

Control of autonomic dysfunction

Many different approaches to the treatment of autonomic dysfunction have been reported. Most are presented as case reports or small series. There is a lack of comparative or controlled studies. In general, outcome measures have been limited to haemodynamic data rather than survival or morbidity. Non-pharmacological methods of preventing autonomic instability rely on *fluid loading* of up to 8 litres day^{-1}.[66 120]

Sedation is often the first treatment. Benzodiazepines, anticonvulsants, and particularly morphine are frequently used. *Morphine* is particularly beneficial as cardiovascular stability may occur without cardiac compromise.[18 93 94] Dosages vary between 20 and 180 mg day^{-1}. Proposed mechanisms of action include replacement of endogenous opioids,[11] reduction in reflex sympathetic activity and release of histamine.[85] Phenothiazines, particularly chlorpromazine are also useful sedatives; anticholinergic and α-adrenergic antagonism may contribute to cardiovasular stability.[58 90]

Initially *β-adrenergic blocking agents*, such as propranolol, were used to control episodes of hypertension and tachycardia,[37 64 90] but profound hypotension, severe pulmonary oedema and sudden death were all found to occur.[17 37 58] Labetolol, which has combined α- and β-adrenergic blocking effects has been used, but no advantage over propranolol was demonstrated (possibly because its α activity is much less than its β activity[31 34]) and mortality remained high.[117] In recent years, the short-acting agent, esmolol, has been used successfully.[68] Although good cardiovascular stability was achieved, arterial catecholamine concentrations remained elevated.

Sudden cardiac death is a feature of severe tetanus. The cause remains unclear but plausible explanations include sudden loss of sympathetic drive, catecholamine-induced cardiac damage and increased parasympathetic tone or 'storms'. Persisting beta block could exacerbate these causes because of negative inotropism or unopposed vasoconstrictor activity, leading to acute cardiac failure, particularly as sympathetic crises are associated with high systemic vascular resistance and normal or low cardiac output. Isolated use of β-adrenergic block with long acting agents, therefore, cannot be recommended.

Postganglionic and *α-adrenergic blocking agents* such as bethanidine, guanethidine, and phentolamine have been successfully used with propranolol,[62 90] along with other similar agents such as trimetaphan, phenoxybenzamine, and reserpine.[87] A disadvantage of this group of drugs is that induced hypotension may be difficult to reverse, tachyphylaxis occurs and withdrawal can lead to rebound hypertension.

The successful management of autonomic disturbance with i.v. *atropine* has been reported.[30] Doses of up to 100 mg h^{-1} were used in four patients. The author argues that tetanus is a disease of acetylcholine excess. He suggests these extremely high doses achieve not only muscarinic but also nicotinic block providing autonomic block, central sedation, and even neuromuscular block. Block of the parasympathetic nervous system was reported to markedly reduce secretions and sweating.

The α_2-adrenergic agonist *clonidine* has been used orally or parenterally, with variable success. Acting centrally, it reduces sympathetic outflow, thus, reducing arterial pressure, heart rate, and catecholamine release from the adrenal medulla.[16] Peripherally, it inhibits the release of norepinephrine from pre-junctional nerve endings. Other useful effects include marked sedation and anxiolysis. Two case reports reported opposing results, one with good control[105] and one with no alteration in haemodynamic instability.[15] Gregorakos used i.v. clonidine 2 μg kg^{-1} tds in 17 of 27 patients treated over 12 yr.[46] The group randomized to receive clonidine had a significantly lower mortality than those receiving conventional treatment.

Epidural[49 104] and *spinal bupivacaine*[102] have been reported to reduce cardiovascular instability. However, catecholamine infusions were required to maintain adequate arterial pressure.

Magnesium sulphate has been used both in artificially ventilated patients to reduce autonomic disturbance[58 72] and in non-ventilated patients to control spasms.[6] Magnesium is a pre-synaptic neuromuscular blocker,[79] blocks catecholamine release from nerves and adrenal medulla,[114] reduces receptor responsiveness to released catecholamines,[79] is an anticonvulsant[119] and a vasodilator.[53] It antagonises calcium in the myocardium and at the neuromuscular junction and inhibits parathyroid hormone release so lowering serum calcium. In overdose, it causes weakness and paralysis,[77] with central sedation[10 82] although the latter is controversial.[58] Hypotension and bradyarrhythmia may occur.[73] It is, therefore, mandatory to maintain levels in the therapeutic range. In the report by James and Manson, patients with very severe tetanus were studied and magnesium was found to be inadequate alone as a sedative and relaxant, but an effective adjunct in controlling autonomic disturbance. Serum concentrations were difficult to predict and regular monitoring of serum magnesium and calcium levels were required.[58] Muscular weakness was apparent and ventilation was required in all cases. Attygalle and Rodrigo[6] studied patients at an earlier stage of the illness yet all cases were probably severe and had undergone tracheostomy. They used similar doses of magnesium to try to avoid sedatives and positive pressure ventilation. They reported successful control of spasms and rigidity. Magnesium concentrations were predictable and readily kept within the therapeutic range, by using the clinical sign of the presence of a patella tendon reflex. In both studies, the absence of hypotension and bradycardia was in contrast to the results with beta block. Both authors agreed that tidal volume and cough may be impaired and secretions increased. Ventilatory support must be immediately available.[7 59] More work is necessary on the role of magnesium both with regard to its physiological effect on neuromuscular function in the presence of tetanus and to establish what role, if any, it has in the routine management of severe tetanus.

Several drugs show potential for use in the future. *Sodium valproate* blocks GABA-aminotransferase, thereby inhibiting GABA catabolism. In animal studies, this prevents the clinical effects of tetanus toxin.[42] *Angiotensin converting enzyme inhibitors* may also help by inhibiting the synthesis of angiotensin II, which increases norepinephrine synthesis and release from the nerve endings.[120] *Dexmedetomidine*, a more potent α_2-adrenergic agonist than clonidine, may also have an effect in reducing sympathetic overactivity.[87] Finally, *adenosine*, which reduces presynaptic norepinephrine release and antagonizes the inotropic effects of catecholamines, has theoretical potential.[87] To date, its clinical use in this setting has not been discussed.

Supportive intensive care treatment

Weight loss is universal in tetanus.[37] Contributory factors include inability to swallow, autonomic induced alterations in gastrointestinal function, increased metabolic rate from pyrexia and muscular activity and prolonged critical illness. Nutrition should, therefore, be established as early as possible. Enteral nutrition is associated with a lower incidence of complications and is cheaper than parenteral nutrition. Percutaneous gastrostomy may avoid the complications associated with nasogastric tube feeding[52] and is easily performed on the intensive care unit under sedation.

Infective complications of prolonged critical illness including ventilator-associated pneumonia are common in tetanus.[46 112] Securing the airway early in the disease and preventing aspiration and sepsis are logical steps in minimizing this risk. As artificial ventilation is often necessary for several weeks[37] tracheostomy is usually performed after intubation. The percutaneous dilatational method[20 47] appears particularly suitable for patients with tetanus.[29 70] This straightforward bedside procedure avoids transfer to and from the operating theatre with the attendant risk of provoking autonomic instability. Prevention of respiratory complications also involves meticulous mouth care, chest physiotherapy, and regular tracheal suction, particularly as salivation and bronchial secretions are greatly increased. Adequate sedation is mandatory before such interventions in patients at risk of uncontrolled spasms or autonomic disturbance and the balance between physiotherapy and sedation may be difficult to achieve.

Other important measures in the routine management of patients with tetanus, as with any long-term critical illness, include prophylaxis of thromboembolism, gastro-intestinal haemorrhage, and pressure sores. The importance of psychological support should not be underestimated.

Complications

Complications are listed in Table 2. These may occur as a result of the disease, for example, laryngospasm; as a consequence of simple treatment, for example, sedation leading to coma, aspiration or apnoea; or intensive treatment, for example, ventilator-associated pneumonia.

Table 2 Complications of tetanus. Life-threatening complications are indicated by an asterisk (*)

Body system	**Complication**
Airway	Aspiration*
	Laryngospasm/obstruction*
	Sedative associated obstruction*
Respiratory	Apnoea*
	Hypoxia*
	Type I* (atelectasis, aspiration, pneumonia) and type II* respiratory failure (laryngeal spasm, prolonged truncal spasm, excessive sedation)
	ARDS*
	Complications of prolonged assisted ventilation (e.g. pneumonia)
	Tracheostomy complications (e.g. tracheal stenosis)
Cardiovascular	Tachycardia*, hypertension*, ischaemia*
	Hypotension*, bradycardia*
	Tachyarrhythmias, bradyarrhythmias*
	Asystole*
	Cardiac failure*
Renal	High output renal failure*
	Oliguric renal failure*
	Urinary stasis and infection
Gastro-intestinal	Gastric stasis
	Ileus
	Diarrhoea
	Haemorrhage*
Miscellaneous	Weight loss*
	Thromboembolus*
	Sepsis and multiple organ failure*
	Fractures of vertebrae during spasms
	Tendon avulsions during spasms

Mortality and outcome

Case fatality rates and causes of death vary dramatically according to the facilities available. Trujillo and colleagues reported a reduction in mortality from 44 to 15% after the introduction of intensive care treatment.[109] In developing countries, without facilities for prolonged intensive care and ventilatory support, deaths from severe tetanus exceed 50% with airway obstruction, respiratory failure, and renal failure as prominent causes. A mortality of 10% has been suggested as an acceptable goal in developed countries.[98] Modern intensive care should prevent death from acute respiratory failure but as a result, in severe cases, autonomic disturbance becomes more apparent. Trujillo reported that 40% of deaths after introduction of ICU care were a result of sudden cardiac death and 15% a result of respiratory complications. Before ICU was established, 80% of historical controls died as a result of early acute respiratory failure.[109] Important complications of ICU care include nosocomial infections, particularly ventilator-associated pneumonia, generalized sepsis, thromboembolism, and gastrointestinal haemorrhage. Mortality varies with patient age. In the USA, mortality in adults below 30 yr may approach zero, but in those over 60 yr is 52%.[78] In Portugal, between 1986 and 1990 all age mortality varied between 32 and 59%.[92] In Africa, mortality from neonatal tetanus without artificial ventilation was reported as 82% in 1960[106] and 63–79% in 1991.[38] With artificial ventilation available this may be as low as 11%[67] but other authors report rates close to 40%.[26]

Severe cases of tetanus generally require ICU admission for approximately 3–5 weeks.[26 37 58 72 92 109 111] Recovery can be expected to be complete, with return to normal function. However, in one of the few follow-up studies in survivors of tetanus, persisting physical and psychological problems were frequent.[55]

Conclusions

Tetanus is fortunately a rare disease in the UK and is entirely preventable by vaccination. It remains a major health problem worldwide. In developed countries, several cases present every year in the elderly and unimmunized population. Mortality in these cases remains high. Prolonged intensive care support may be necessary but most treatment is based on limited evidence. Major therapeutic challenges lie in the control of muscular rigidity and spasms, the treatment of autonomic disturbance and the prevention of complications associated with prolonged critical illness. Return to normal function can be expected in those who survive.

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SHORT COMMUNICATIONS

Identification of polysubstance abuse in the parturient

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Illicit drugs are widely used by inner city patients and their use by pregnant women has increased in recent years. The aim of this study was to determine the prevalence of polysubstance abuse among parturients at our institution who received no prenatal care ('unbooked') and to determine the accuracy of the Ontrak TesTcup™ an *in vitro* immunodiagnostic assay. We prospectively analysed urine from 50 'unbooked' parturients and found that 26 (52%) tested positive for cocaine. Of these, six patients (23%) were also positive for morphine. All TesTcup™ results were confirmed by the hospital laboratory using alternate chemical methods. When comparing TesTcup™ to the hospital laboratory, there were no false positive or negative results. Given the high frequency of concomitant opioid abuse in cocaine-abusing parturients, anyone suspected of cocaine abuse should be tested for other illicit substances. TesTcup™ is a clinically accurate test that allows the rapid assessment of several drugs of abuse, which may impact on anaesthetic care.

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Illicit substance abuse among women of reproductive age has increased over the past decade.[1] Patients who have received no prenatal care ('unbooked') are at the highest risk for substance abuse. For example, the prevalence of antepartum cocaine use among 'unbooked' parturients at a hospital in New York City was reported to be 68%.[2] Pregnant women who use illicit drugs may be more likely to use a combination of drugs rather than a single drug.[3] The aim of this study was to determine the prevalence of polysubstance abuse among unregistered parturients at our institution and to evaluate the accuracy of a screening test (TesTcup™) that would provide simultaneous toxicology results for several drugs of abuse.

Methods and results

The official policy of this hospital is to perform mandatory urine toxicology testing on all 'unbooked' patients admitted to our maternity unit. The patients are informed of this policy and that these results will become part of their hospital record. The results will be used by physicians as well as social workers to assist in discharge planning for the baby. In this study, toxicology testing was limited to these 'unbooked' patients, as they are easily identifiable and at high risk for antepartum drug abuse.[2]

Following Institutional Review Board approval, urine from 50 consecutively admitted 'unbooked' parturients that was being sent to the hospital laboratory for toxicology testing was also tested by one anaesthetist using the Ontrak TesTcup™ (Roche Diagnostic Systems, Branchburg, NJ, USA). This is a qualitative assay for cocaine metabolite (benzoylecgonine), opioids (morphine and its derivatives), amphetamine, tetrahydrocannabinol (THC), and phencyclidine (PCP), a ketamine-like drug. Toxicology results obtained by the anaesthetist were compared with those of the hospital laboratory, performed by enzyme immunoassay techniques according to manufacturer's specifications.

The TesTcup™ comprises immunochromatographic reagents that qualitatively and simultaneously detect the presence of illicit substances or their metabolites in the urine. It is based on the competition between the drug and the immobilized drug conjugate in the sample for anti-drug antibodies coated on blue-dyed microparticles. Each drug assay has its own immunochromatographic strip, which contains an antibody specific for each illicit substance or metabolite.[4] In approximately 3–5 min, a control reading for

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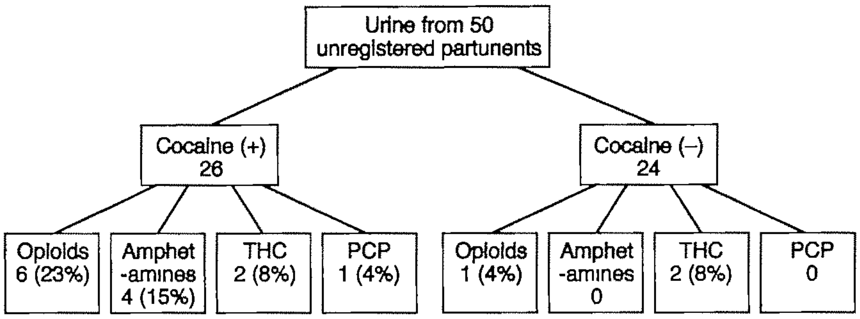

Fig 1 Profile of polysubstance abuse in 'unbooked' parturients (n=50). THC=tetrahydrocannabinol, PCP=phencyclidine

each substance is automatically performed and appears in the lower part of the result panel on the front of the cup. Following this, the various toxicology results can be easily read by the presence or absence of blue bands in the result window, similar to those used in commonly available over-the-counter pregnancy tests. The cost of each TesTcup™ is approximately 20.00 US dollars. The anaesthetist performing the assay was blinded to the results of the hospital laboratory. The TesTcup™ and hospital test results were compared by kappa analysis.

Of the 50 urine samples analysed by the TesTcup™, 26 (52%) were positive for cocaine, seven (14%) were positive for opioids, four (8%) were positive for amphetamines, four (8%) were positive for THC, and one (2%) was positive for PCP. Of the 26 samples positive for cocaine, six (23%) were also positive for opioids, four (15%) were positive for amphetamines, two (8%) were positive for THC, and one (4%) was positive for PCP (Fig. 1). These results were all confirmed by testing in the hospital laboratory, with no false positive or false negative results (kappa=1). All patients who tested positive for opioids denied opioid use, and 13 of the 26 patients whose samples tested positive for cocaine denied cocaine use. As none of the opioid positive parturients had evidence of needle marks, it is likely that the opioids were combined with other illicit agents and smoked or taken orally.

Comment

Identification of the substance-abusing parturient presents a challenge as denial of such abuse is common and clinical signs of illicit drug use can mimic other diseases such as pre-eclampsia.[5] In our study, 52% of the unregistered parturients who were admitted to the maternity unit tested positive for cocaine, and of these 23% also tested positive for opioids. The majority of parturients who tested positive for illicit drugs denied substance abuse. Our findings are consistent with the results of previous studies that screened either parturients or neonates for illicit substances.[6 7]

Although knowledge of cocaine abuse in the parturient is vital to the anaesthetist,[2] information regarding opioid abuse is equally important. Parturients requesting analgesia in labour are increasingly likely to receive spinal or epidural opioids. If side effects of this treatment occur, antagonist or agonist-antagonist agents may be administered. In addition, agonist-antagonist agents such as nalbuphine and butorphanol are sometimes administered for analgesia in labour. The administration of these drugs represents a potential hazard for the unidentified opioid-dependent parturient as they can precipitate acute maternal and/or fetal withdrawal syndrome.[8]

Because of the potential obstetric and anaesthetic implications of drug abuse, all parturients considered to be 'high risk' should be tested with a method that allows for prompt results. Hospitals with toxicology screening procedures often analyse samples using gas chromatography/mass spectrometry or thin-layer chromatography, and fluorescence polarization immunoassays. While these are extremely accurate methods, results may not be available for more than 24 h, depending on hospital facilities. This is generally too late to be of benefit to the anaesthetist caring for these patients.

We evaluated a rapid and inexpensive screening test that was found to identify illicit substances that had been ingested within the previous 72 h. The TesTcup™ has been shown to be an accurate assay[9] and has been utilized by many specialties and in emergency situations.[10] In this study, an anaesthetist without special training in toxicology testing was able to complete the tests in less than 5 min with results identical to those reported by the hospital laboratory. It should be noted, however, that latex agglutination tests do not provide a quantitative analysis. Although a positive result identifies patients who have ingested specific illicit drugs up to 72 h before testing, these tests cannot quantify the amount of drug or identify the time of last ingestion. Rather, the TesTcup™ identifies either drug or drug metabolites only if they have reached a predetermined cut-off level. As the half-life of cocaine, is only minutes in duration, benzoylecgonine, a longer acting primary metabolite of cocaine is used for detection of this drug. It is possible that below the cut-off limits, TesTcup™ results might be negative despite presence of low levels of drug or drug metabolite. However, at such levels, clinical significance is questionable. When time allows, recognized laboratory testing for drugs of abuse is optimal. However, when toxicology results are necessary in an emergency situation such as the parturient in active labour, immunodiagnostic assays such as the TesTcup™ can provide accurate information that can be used by the anaesthetist to provide optimal care.

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Stress response during weaning after cardiac surgery

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We compared the effects of weaning using synchronized intermittent mandatory ventilation (SIMV) with the use of biphasic positive airway pressure (BIPAP) on the stress response, oxygen uptake ($\dot{V}_{O_2}$) and work of breathing (WOB) in 10 patients after aortocoronary bypass surgery. All three ventilatory settings were investigated in each patient, for example, volume-controlled mechanical ventilation immediately before weaning was followed, in randomized order, by both SIMV and BIPAP. In addition to routine monitoring of continuous and respiratory state, we measured $\dot{V}_{O_2}$, WOB, and pressure–time product (PTP) as well as the plasma concentrations of epinephrine, norepinephrine, ACTH, cortisol, vasopressin, and prolactin. Although respiratory rate (*f*), WOB and PTP were greater with both SIMV and BIPAP when compared with control, other variables did not change with the ventilatory mode. In conclusion, weaning from mechanical ventilation using partial support modes does not affect the postoperative stress response in patients who have had uncomplicated cardiac surgery.

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The effect of weaning on the postoperative stress response in surgical patients is uncertain. In these circumstances, oxygen consumption ($\dot{V}_{O_2}$) and plasma catecholamine levels are considered to be determined by and related to the work of breathing (WOB).[1 2] The effects of sedation and the ventilator mode need to be clarified.

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Oxygen consumption and cardiac index increase in patients during weaning from mechanical ventilation after cardiac surgery,[3] and the additional load on the cardiovascular system could be crucial in some patients. To study the underlying mechanisms we measured $\dot{V}_{O_2}$, WOB, cardiovascular effects, and the plasma concentrations of catecholamines and other hormones involved in the stress response during weaning using different ventilatory modes, in patients who had aortocoronary bypass surgery.

Methods and results

After approval by the local ethical committee we studied 10 patients who gave written informed consent. They were admitted to the intensive care unit (ICU) after aortocoronary bypass surgery. Inclusion criteria were as defined in a previous study.[4] Anaesthesia was obtained with i.v. propofol (2 mg kg^{-1} bolus followed by a continuous infusion of 25–75 µg kg^{-1} min^{-1}), fentanyl (40–80 µg kg^{-1}) and muscle relaxation obtained with pancuronium bromide (0.2–0.3 mg kg^{-1}). After operation, a propofol infusion (25–50 µg kg^{-1} min^{-1}) was used for sedation.

Mechanical ventilation was with an EVITA-2 ventilator (Drägerwerk AG, Lübeck, Germany) using the following settings: volume-controlled continuous positive pressure ventilation (CPPV), tidal volume (V_T=8–10 ml kg^{-1}, and respiratory rate (f)=10 breaths min^{-1}) until rewarming and recovery from anaesthesia was complete. If cardiovascular measurements were stable and no surgical complications had occurred, a set of control data was obtained as described below. The propofol infusion was then stopped. As soon as the patients were able to breathe spontaneously at a respiratory rate of 10–25 breaths min^{-1}, the ventilator was set according to a preset random order (which was masked for the physicians involved in patient care) to one of the two study settings, for example, synchronized intermittent mandatory ventilation (SIMV) or biphasic positive airway pressure (BIPAP), both combined with inspiratory pressure support (PS). The mechanical respiratory rate (f_{SIMV}) was reduced to 5 breaths min^{-1}, and the pressure support adjusted to give a V_T of about 50% of the passive mechanical breaths. During SIMV the V_T was set as during CPPV, whereas during BIPAP the inspiratory pressure level (P_{insp}) was set to the plateau inspiratory pressure noted during CPPV. At least 120 min after the propofol infusion had been stopped, a set of data was obtained. We then switched to the other test mode and sampled data again after 60 min.

We recorded the following variables:

- Flow, airway pressure and oesophageal pressure (measured from a balloon catheter inserted using a laryngoscope immediately after induction of anaesthesia and positioned using the 'occlusion test'[4]), as continuously digitised values to allow off-line calculation of respiratory rate (f), minute ventilation (MV), pressure–time product (PTP), and WOB methods described previously.[5]
- Heart rate (HR), systemic vascular pressure, and cardiac index (CI).
- $\dot{V}_{O_2}$ ($\dot{V}_{O_2\,measured}$), carbon dioxide production rate ($\dot{V}_{CO_2}$), respiratory quotient (RQ=$\dot{V}_{CO_2}/\dot{V}_{O_2\,measured}$) and mean expired P_{CO_2} using the Deltatrac® metabolic monitor (Datex Corp., Helsinki, Finland).
- Arterial and mixed venous blood gases for the calculation of venous admixture ($\dot{Q}_S/\dot{Q}_T$), dead space ventilation (V_D/V_T) and $\dot{V}_{O_2}$ ($\dot{V}_{O_2\,calculated}$) according to standard equations and the Fick principle, respectively.
- Plasma levels of epinephrine, norepinephrine, ACTH, cortisol, vasopressin and prolactin using methods previously described.[6 7]

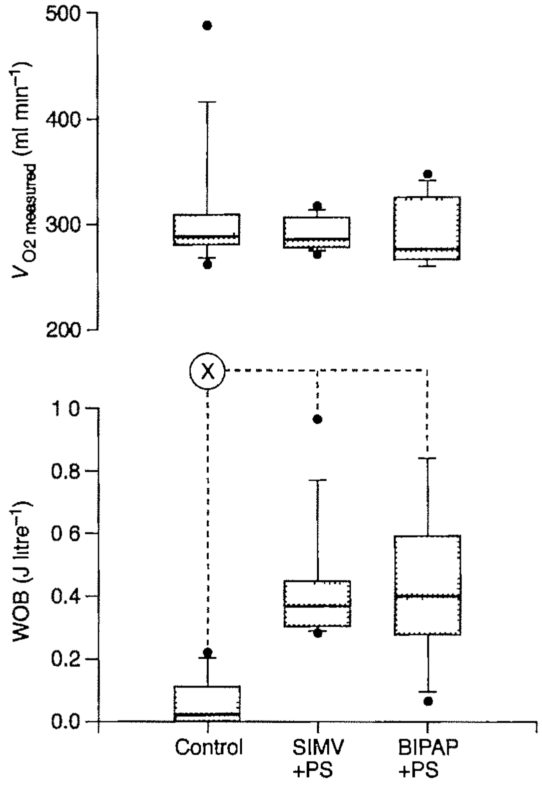

Fig 1 The box plots show the work of breathing (WOB, lower panel) and oxygen consumption as measured by the Deltatrac® device ($\dot{V}_{O_2\,measured}$, upper panel) during the different study conditions The boxes represent medians (horizontal lines in each box) and quartiles. Five and 95% percentiles are indicated by the error bars. Single values outside of the percentile-ranges are drawn as dots The circled 'X' sign indicates the statistically significant difference between the WOB measured during volume-controlled mechanical ventilation (control condition) and either of the two test-modes corresponding to SIMV+PS and BIPAP+PS.

Statistical analysis was performed using a Friedman rank-sign analysis for repeated measures and a subsequent non-parametric Student Newman–Keuls test.

All data are presented as medians and quartile values in Table 1. Although cardiovascular and gas exchange

Table 1 All values are medians, with quartile values $^*P<0.05$ control *vs* SIMV+PS and BIPAP+PS, respectively (Friedman rank sign analysis for repeated measures, followed by non-parametric Student Newman–Keuls test). Abbreviations are: HR=heart rate, MAP=mean arterial pressure; CI=cardiac index; *AVD*o2=arterial-venous oxygen content difference; Pa_{O_2}=arterial oxygen partial pressure, Pa_{CO_2}=arterial carbon dioxide partial pressure; *QS*/*QS*=venous admixture; *VD*/*VT*=dead space ventilation, $V_{O_2\,\text{calculated}}$=oxygen consumption calculated according to Fick's principle; $V_{O_2\,\text{measured}}$=oxygen consumption measured by means of indirect calorimetry, V_{CO_2}=carbon dioxide production, RQ=respiratory quotient which equals the ratio $\dot V_{CO_2}/V_{O_2\,\text{measured}}$, *f*=respiratory rate, MV=minute ventilation; WOB=work of breathing; PTP=pressure-time product. Normal plasma concentrations of hormones are epinephrine 12–110 pg ml^{-1}; eorepinephrine 120–520 pg ml^{-1}; ACTH 9–25 pg ml^{-1}; cortisol 5–25 μg 100 ml^{-1}; vasopressin <6.7 pg ml^{-1}, prolactin 5–15 ng ml^{-1} (male) and 5–25 ng^{-1} ml (female)

	Control	**SIMV+PS**	**BIPAP+PS**
HR (beats min^{-1})	91 (87,97)	84 (78,98)	89 (84;92)
MAP (mm Hg)	83 (75,86)	77 (72;81)	78 (73;80)
CI (litre min^{-1} m^2)	3.4 (3.1;3.5)	3.5 (3.0;3.8)	3.6 (3.4,4.1)
$AVDo_2$	3.6 (3.1,4.3)	3.7 (3.3,4.4)	3.6 (3.1;4.1)
Pa_{O_2}	109 (100,122)	106 (94,125)	95 (92,108)
Pa_{CO_2}	40 (38;41)	43 (42,44)	43 (42;43)
Q_S/Q_T (%)	6.4 (4.5,7.1)	4.2 (3.9,5.3)	5.6 (5.2,6.5)
V_D/V_T (%)	36 (35,39)	38 (36;42)	39 (38,44)
$V_{O_2\,\text{calculated}}$ (ml min^{-1})	241 (227;288)	247 (227,269)	247 (221;280)
$V_{O_2\,\text{measured}}$ (ml min^{-1})	286 (279;305)	287 (278;306)	276 (262;316)
V_{CO_2}	206 (193,230)	200 (191;212)	209 (193,212)
RQ	0.71 (0.70,0.75)	0.71 (0.67,0.72)	0.73 (0.71;0.76)
f (breaths min^{-1})	10 (9;12)*	14 (12,17)	15 (12;18)
MV (litre min^{-1})	6.6 (6.0;7.6)	7.0 (6.4,7.6)	7.9 (7.2,8.4)
WOB (J $litre^{-1}$)	0.0 (0.0,0.17)*	0.37 (0.30,0.44)	0.40 (0.29;0.56)
PTP (cm H_2O s min^{-1})	3 (0,9)*	59 (53,66)	79 (59,90)
Temperature (°C)	37.3 (36.5;37.4)	37.5 (37.2,37.6)	37.6 (37.5;37.8)
Epinephrine (ng $litre^{-1}$)	283 (167,373)	208 (135;346)	237 (209,256)
Norepinephrine (ng $litre^{-1}$)	735 (507;1185)	788 (502,1054)	725 (467;1034)
ACTH (ng $litre^{-1}$)	599 (234;820)	533 (100,708)	593 (99,905)
Cortisol (μg 100 ml^{-1})	14 (12;17)	16 (13,19)	15 (14;19)
Vasopressin (ng $litre^{-1}$)	51 (30,92)	54 (33;62)	56 (37,96)
Prolactin (ng ml^{-1})	1.0 (0.7;1.9)	1.0 (0.7;1.6)	0.8 (0.8,1.3)

measurements were in the normal range during all study conditions, plasma values of catecholamines and hormones, except for cortisol and prolactin (probably partly suppressed by the low-dose dopamine-infusion administered during weaning from cardiopulmonary bypass), were elevated regardless of the ventilatory mode used during the corresponding test period. The values noted in the three study conditions, however, were not statistically significant. *f*, WOB, and PTP were greater during both partial ventilation support modes than during control. However, no statistically significant differences were found when comparing SIMV+PS with BIPAP+PS.

Comment

Wet set out to measure $\dot V_{O_2}$ and the stress hormone response at the same time during weaning after cardiac surgery. Compared with previous measurements in intubated, spontaneously breathing patients,[4] WOB and PTP were less with both modes SIMV and BIPAP because of the greater degree of mechanical support applied. Nevertheless, we showed that both ventilatory modes required the patients to sustain a significant portion of their minute ventilation. The patients were sufficiently awake to completely control their own breathing pattern, as seen from their respiratory rates. Interestingly, $\dot V_{O_2}$ did not increase when WOB was increased after switching to either SIMV or BIPAP, indicating that spontaneous breathing was performed efficiently, with a minimal influence on the cardiovascular system.[1] This finding was independent of the method used to determine $\dot V_{O_2}$. The difference between $\dot V_{O_2\,\text{measured}}$ and $\dot V_{O_2\,\text{calculated}}$ was probably related to the pulmonary oxygen uptake, which $\dot V_{O_2\,\text{calculated}}$ does not measure. Therefore, using the Fick method to measure total body $\dot V_{O_2}$ after cardiopulmonary bypass may underestimate the true value by up to 20–30%.[8]

The catecholamine and stress hormone blood concentrations we found generally were greater than normal and also greater than values previously measured after abdominal surgery.[6] The hormone release may have contributed to haemodynamic stability as was demonstrated in that study.[6] These catecholamine and hormone concentrations were already present in the control period and did not increase after withdrawal of sedation and switching from passive ventilation to partial spontaneous breathing. Therefore, we believe that after cardiac surgery the hormonal response is not affected by the discomfort of breathing. Even BIPAP, which can make breathing more comfortable during weaning and reduce the need for sedative drugs[9] did not affect the plasma catecholamine and stress hormone levels.

The hormonal stress response may provide an objective method to measure patient comfort during mechanical ventilation. It has been used successfully in preterm infants to demonstrate the advantage of mechanically supported spontaneous breathing over controlled mechanical ventilation in terms of reduced stress response.[10] Assessment of the attempt to determine the physiologic stress response during weaning by measuring stress hormone blood concentrations in adults have not been attempted before.

We found that during the early stages of weaning from mechanical ventilation after cardiac surgery, switching from passive ventilation to partial spontaneous breathing and interruption of continuous sedation did not alter the postoperative hormonal stress response and $\dot{V}_{O_2}$. Obviously, since we studied a small group of subjects after uncomplicated heart surgery, without pre-existing pulmonary diseases and limited myocardial function, the results may not apply to patients with compromised circulatory or respiratory function or if weaning from prolonged mechanical ventilation.

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Effects of portal triad clamping on haemodynamic conditions during laparoscopic liver resection

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To evaluate the haemodynamic effects of portal triad clamping (PTC) during laparoscopic liver resection, 10 patients without cardiac disease were studied by invasive monitoring including a pulmonary artery catheter and were compared with a control group of 10 patients undergoing liver resection by laparotomy. During laparoscopic surgery, intra-abdominal pressure was kept below 14 mm Hg and minute ventilation was adjusted to prevent hypercapnia. Measurements were made before PTC (T1), 5 min after PTC (T2) and 5 min after clamp release (T3). During clamping with pneumoperitoneum, mean arterial pressure (MAP) remained stable (+2%; not significant), systemic vascular resistance (SVR) increased by 37% (P<0.01, T2 *vs* T1) and cardiac index (CI) decreased by 19% (P<0.01, T2 *vs* T1). During laparotomy and clamping, MAP

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increased by 18% ($P<0.01$, T2 *vs* T1), SVR increased by 36% ($P<0.01$, T2 *vs* T1) and CI decreased by 9% (not significant). We were unable to demonstrate a difference in haemodynamic changes during clamping with pneumoperitoneum *vs* the open surgical technique, but in a small number of patients this lack of difference could have been a result of inadequate statistical power. The haemodynamic changes that we found were well tolerated in these patients, who had normal cardiac function.

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With greater experience in both laparoscopy and liver surgery, laparoscopy for some liver resections is now feasible and safe.[1] During open abdominal liver surgery, portal triad clamping (PTC) can limit bleeding.[2] Portal triad clamping typically increases mean arterial pressure (MAP) (+21%) and systemic vascular resistance (SVR) (+48%), and decreases cardiac output (–17%).[3] Similar haemodynamic changes occur at the start of peritoneal insufflation.[3 4] Some authors found the changes caused by pneumoperitoneum similar to those of chronic heart failure.[5] As laparoscopic liver resection results in both types of change, potentially serious haemodynamic changes may occur.

We studied PTC performed during laparoscopy and compared the haemodynamic responses with the responses to PTC during laparotomy, and assessed the possible adverse effects of such changes.

Methods and results

After approval of the study by the investigational review board,[1] patients were informed about the innovative nature of the procedure and their consent was obtained. Patients with left atrial dilation (>4.0 cm), left ventricular dilation (left ventricular end-diastolic internal dimensions >5.7 cm), decreased shortening fraction (<31%), regional wall motion abnormalities, valvular heart disease, cardiomyopathy and pericardial disease were excluded from the study. We also excluded patients who had intraoperative bleeding, defined as the need for rapid volume expansion or blood transfusion before PTC, and patients with haemodynamic instability, defined as MAP variation greater than 10% before PTC.

Between May 1999 and February 2000, we studied 10 consecutive adult patients undergoing elective liver resection done laparoscopically (laparoscopy group). The liver segments that can be safely resected laparoscopically are the anterior and lateral segments (segments II–VI).[1] Laparoscopic resection was performed for peripheral lesions 5 cm or less in size, and resections were limited to three segments or fewer.[1] Tumours in posterior and superior segments (i.e. segments I, VII and VIII) should not be considered because of difficult laparoscopic access and connections with the inferior vena cava and major hepatic veins.[1]

Table 1 Patient characteristics Unless otherwise stated, results are expressed as mean (SD) for continuous variables. *P* values are reported when <0.2, otherwise the difference is indicated as being not significant (NS)

Characteristic	Laparoscopy group	Open group	*P*
Age (yr)	58 1 (36–79)	65 6 (40–76)	0.2
Sex (M/F)	7/3	8/2	NS
Body surface area (m^2)	1 76 (0.22)	1.8 (0.20)	NS
Arterial hypertension (*n*)	1	4	NS
Cirrhosis (*n*)	5	2	NS
Pathological diagnoses (*n*)			
Primary liver cancer	7	5	
Secondary liver cancer	0	5	
Benign liver lesion	3	0	0 1
Blood loss (ml) (median, 25th and 75th percentiles)	400 (275, 1000)	600 (400, 600)	NS
Total i v. infusion (ml kg^{-1})	43.4 (17.7)	36.9 (11 8)	NS
Transfusion (*n*)	1	0	NS
Duration of surgery before PTC (min)	100 (44)	102 (48)	NS

Table 2 Comparisons of haemodynamic measurements in the laparoscopy (L) and open (O) groups before, during and after PTC. T1=5 min before portal triad clamping (PTC); T2=5 min after clamping, T3=5 min after clamp release. MAP=mean arterial pressure; HR=heart rate, RAP=right atrial pressure, PAOP=pulmonary artery occlusion pressure, MPAP=mean pulmonary artery pressure, CI=cardiac index; SVR=systemic vascular resistance; PVR=pulmonary vascular resistance. CI, SVR and PVR were calculated according to standard formulae. *Intergroup comparison, $P<0.05$. T2 *vs* T1†=$P<0.05$ at T2 *vs* T1, T3 *vs* T2†=$P<0.05$ at T3 *vs* T1. *P* values are reported when <0.2, otherwise the difference is indicated as being not significant (NS)

Variable	T1		T2		T3		ANOVA results	
	Group L	Group O	Group L	Group O	Group L	Group O	Group L	Group O
MAP (mm Hg)	84 (13)	92 (12)	84 (8)	108 (19)*	83 (8)	96 (13)	NS	T2 *vs* T1† T3 *vs* T2†
HR (beats min^{-1})	73 (12)	82 (14)	73 (11)	80 (15)	74 (10)	78 (13)	NS	NS
RAP (mm Hg)	9.0 (4.6)	7.6 (3.2)	7.4 (4.6)	6.0 (1.8)	9.5 (6.0)	6.6 (3.4)	0.12	0.13
PAOP (mm Hg)	11.5 (4.7)	11.3 (2.0)	11.5 (5.5)	10.1 (2.0)	12.8 (5.2)	11.2 (3.4)	NS	NS
MPAP (mm Hg)	21 (6)	20 (2)	20 (5)	18 (3)	23 (7)	20 (5)	T3 *vs* T2†	NS
CI (litre min^{-1} m^{-2})	3.6 (1.5)	3.8 (1.2)	2.8 (1.3)	3.6 (1.9)	3.5 (1.1)	3.7 (1.1)	T2 *vs* T1† T3 *vs* T2†	NS
SVR (dyne s cm^{-5} m^{-2})	1846 (520)	1899 (596)	2480 (779)	2705 (1330)	1797 (489)	2062 (569)	T2 *vs* T1† T3 *vs* T2†	T2 *vs* T1† T3 *vs* T2†
PVR (dyne s cm^{-5} m^{-2})	258 (159)	202 (85)	272 (116)	189 (93)	262 (136)	184 (74)	NS	NS

The carbon dioxide pneumoperitoneum was induced with 14 mm Hg intra-abdominal pressure in the supine position before a 20° head-up tilt. A control group of 10 consecutive patients undergoing liver resection performed via an abdominal incision (open group) was studied similarly. Intermittent PTC was applied with 15-min clamping and 5-min release periods.[6]

Anaesthetic management and intraoperative care were standardized throughout the study. General anaesthesia was induced with thiopental 4–6 mg kg^{-1} and sufentanil 0.3 μg kg^{-1} i.v. After orotracheal intubation, facilitated with atracurium 0.5 mg kg^{-1}, anaesthesia was maintained with 0.5–1.5% end-tidal isoflurane together with a continuous infusion of sufentanil 0.3 μg kg^{-1} h^{-1}, and muscular relaxation was maintained by a continuous infusion of atracurium 0.5 mg kg^{-1} h^{-1}. Crystalloid solution was infused during operation at a basal rate of 10 ml kg^{-1} h^{-1}. The inspired oxygen fraction was set at 50% in air and minute ventilation was adjusted to maintain arterial carbon dioxide below 45 mm Hg.

After induction of general anaesthesia, one radial artery was cannulated and a 7.5 F thermodilution Edwards Swan–Ganz catheter (Baxter, Irvine, CA, USA) was introduced via the right internal jugular vein. Pressures were obtained after calibration, zeroing to atmospheric pressure and using the midchest level as reference. We recorded MAP, pulmonary artery pressure, right atrial pressure and pulmonary artery occlusion pressure, all at end-expiration. Cardiac output was measured using the thermodilution technique, and an extent of variation less than 10% was considered permissible when taking the average of three measurements.

The first period of PTC during the surgical procedure was studied. Haemodynamic data were collected 5 min before PTC (T1), 5 min after clamping (T2) and 5 min after clamp release (T3) in the two groups.

Data were analysed with the Statview 5.0 statistical packages (SAS Institute, Cary, NC, USA). Data are presented as mean (SD) unless otherwise stated. Intergroup comparisons were made with the χ^2 test or Fisher's exact test for categorical variables, and Student's *t*-test or the Mann–Whitney *U*-test when appropriate for continuous variables. Changes in variables within the two groups were subjected to analysis of variance (ANOVA) followed by the Neuman–Keuls test, as appropriate. Assuming a decrease in CI of 30% to be clinically important, we estimated that 10 patients in each group would be adequate to test the null hypothesis at 0.05 significance with a power of 0.83. A *P* value <0.05 was considered statistically significant.

Study population

The two groups of patients were similar in clinical characteristics, duration of surgery before PTC, blood loss and total i.v. infusion (Table 1). No severe perioperative cardiopulmonary complications were observed. No vasoactive drugs were used during PTC. All patients recovered uneventfully, except for one patient who had nosocomial Legionnella pneumonia but recovered satisfactorily.

Haemodynamic values during PTC

At the time of data recording, body temperature was 34.8 (0.54)°C in the laparoscopy group and 35.1 (0.63)°C in the open group (not significant). Peak airway pressure was greater in the laparoscopy group [25 (4) *vs* 19 (2) cm H_2O, $P<0.003$], as was $P\text{CO}_2$, although this remained below 40 mm Hg. The pH value lay between 7.36 and 7.43 in both groups. The haemoglobin concentration was 11.6 (1.7) g dl^{-1} in the laparoscopy group and 12.5 (1.8) g dl^{-1} in open group (not significant), and remained stable throughout the PTC period.

Before PTC, haemodynamic values were similar in the two groups. In the laparoscopic procedures, during PTC, MAP remained stable [2 (11)%, not significant], SVR rose by 37 (45)% (T2 *vs* T1, $P<0.01$) and CI decreased by 19 (17)% (T2 *vs* T1, $P<0.01$) (Table 2). In the open procedures, during PTC, MAP increased by 18 (18)% (T2 *vs* T1, $P<0.01$), SVR increased by 36 (28)% (T2 *vs* T1, $P<0.01$) and CI decreased by 9 (16)% (not significant) (Table 2). There were no differences between the two groups other than a moderate increase in MAP in open group [open group, 108 (19) mm Hg; laparoscopy group, 84±8 mm Hg; $P<0.05$].

Comment

In our study, the haemodynamic changes associated with PTC during open procedures were less pronounced than those observed by Delva *et al.*[3] but were similar to those of a recent study.[6] The anaesthetic technique could have affected these haemodynamic changes, as isoflurane was used in our study instead of enflurane in the study of Delva *et al.*[3] Dramatic haemodynamic changes after PTC during pneumoperitoneum have been reported in a pig model,[7] with marked decreases in CI and MAP and an increase in heart rate.[7] We found that the haemodynamic response was different in humans.

In the present study, conditions before PTC were similar in the two groups despite the pneumoperitoneum. Pneumoperitoneum causes increases in arterial pressure and SVR.[4] Changes in cardiac output are variable, consistent with the Starling resistor concept of abdominal venous return.[8] Moreover, the reverse Trendelenburg position causes a further decrease in preload.[4] However, these haemodynamic changes were not sustained throughout the period of pneumoperitoneum.[4] The partial correction of the haemodynamic variables during pneumoperitoneum may have been caused by the vasodilating properties of isoflurane.[4]

In fact, PTC during laparoscopy did not cause significant haemodynamic changes compared with the open procedures. The MAP was stable, CI decreased slightly and SVR increased. We suggest that an increase in SVR counteracted the moderate decrease in CI, so that MAP remained at the preclamping level. The mild decrease in CI could be explained by a preload that was insufficient[3 8] to compensate for the increased stroke work necessary to maintain cardiac output.[9] During the laparotomy, the normal heart could become sensitive to changes in afterload, as in heart failure.[5 10] The mild decrease in CI during PTC performed under laparoscopy can be explained by a decrease in venous return and/or an increase in SVR. These haemodynamic changes were not great enough to necessitate stopping the procedure or to release the PTC.

In conclusion, in a small number of patients, we could not find a difference in haemodynamic changes during PTC during laparotomy, and PTC carried out during an open surgical procedure. However, this lack of difference could be a result of inadequate power of the study. Laparoscopic liver resections with PTC are feasible and safe in patients with normal cardiac function.

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Arterial and mixed venous xenon blood concentrations in pigs during wash-in of inhalational anaesthesia†

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There are no data available on the kinetics of blood concentrations of xenon during the wash-in phase of an inhalation anaesthesia aiming at 1 MAC end-expiratory concentration. Therefore, we anaesthetized eight pigs with continuous propofol and fentanyl and measured arterial, mixed venous and end-expiratory xenon concentrations by gas chromatography–mass spectrometry 1, 2, 3, 4, 5, 7, 10, 15, 20, 30, 60 and 120 min after starting the anaesthetic gas mixture [67% xenon/33% oxygen; 3 litre min^{-1} during the first 10 min, thereafter minimal flow with 0.48 (SD 0.03) litre min^{-1}]. End-expiratory xenon concentrations plateaued (defined as <5% change from the preceding value) at 64 (6) vol% after 7 min, and arterial and mixed venous xenon concentrations after 5 and 15 min respectively. The highest arterio-venous concentration difference occurred after 3 min. Using the Fick principle, we calculated a mean xenon uptake of 3708 (829) and 9977 (3607) ml after 30 and 120 min respectively.

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Keywords: anaesthestic techniques, inhalation; anaesthetics, gases, xenon; pharmacokinetics, xenon; pig

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The inert gas xenon is under investigation as an alternative to nitrous oxide as an inhalational anaesthetic. Being an almost ideal anaesthetic, xenon offers several potential advantages over classical inhalational agents.[1] The low blood/gas partition coefficient (0.11)[2] leads to rapid wash-in and induction and emergence from anaesthesia.[3 4] In order to define precisely the kinetics of the wash-in phase of inhalational anaesthesia with xenon and to estimate its expenditure during 2 h of anaesthesia with a standard semi-closed anaesthesia circuit, we measured end-expiratory gas, arterial and mixed venous blood concentrations by gas chromatography–mass spectrometry.

Methods and results

As part of another protocol approved by the institutional animal care committee (Regierungspräsidium, Tübingen, Germany) and performed in accordance with the legal regulations for the use of laboratory animals, which investigated the effects of different anaesthesia techniques during experimental bowel obstruction, eight pigs aged 12–16 weeks and weighing 37.5–46 (SD 3 2) kg were premedicated with azaperon 4 mg kg^{-1} i.m. and atropine 2.5 mg i.m. Anaesthesia was induced with i.v. ketamine 2 mg kg^{-1} and pentobarbitone 8–10 mg kg^{-1}. The trachea was intubated and ventilation was performed with 30% oxygen in nitrogen using a standard semi-closed ventilator (Cicero; Draegerwerk, Lübeck, Germany). Ventilatory settings throughout the experiment were tidal volume (V_T) 10–14 ml kg^{-1} (adjusted to achieve a Pa_{CO_2} of 37–43 mm Hg), ventilator frequency (f) 12 min^{-1}, and a positive end-expiratory pressure of 5 cm H_2O. Muscle paralysis was obtained with alcuronium dichloride (0.25 mg kg^{-1}) followed by an infusion (14 mg h^{-1}). Anaesthesia was maintained with a continuous i.v. infusion of propofol (5–10 mg kg^{-1} h^{-1}) and fentanyl (5–10 µg kg^{-1} min^{-1}). Depth of anaesthesia was assessed by continuous EEG monitoring (Neurotrac; Interspec, Cronshocken, PA, USA); the 95% spectral edge frequency was always below 15 Hz during the experiment. Ringer's solution (7 ml kg^{-1} h^{-1}) was administered continuously as a maintenance fluid. A thermodilution pulmonary artery catheter was placed via

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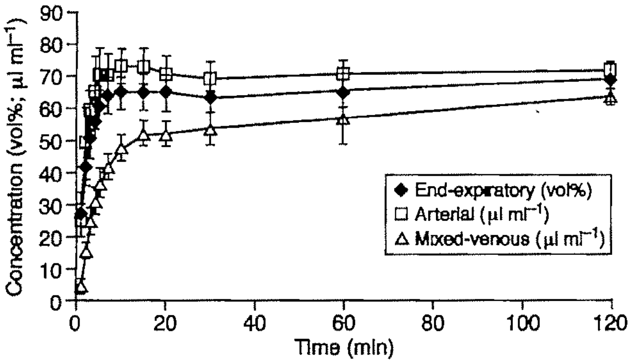

Fig 1 End-expiratory (vol%) and arterial and mixed venous blood (μl ml^{-1}) concentrations of xenon Data are mean ±SD.

the right internal jugular vein, and both femoral arteries were exposed to insert a catheter for blood sampling and continuous recording of arterial pressure. A 3 Fr thermistor-tipped fibre-optic catheter was used for measurement of cardiac output by thermal dye double indicator (indocyanine green) dilution and for the determination of intrathoracic blood volume (FT-Pulsiocath PV 2023, Cold Z021; Pulsion, München, Germany). A minimum of 2 h was allowed for recovery after the surgical procedure. For the measurement of minute volume, a rotating vane flowmeter was used as an independent volumeter because of the inaccuracy of the built-in volumeter of the anaesthesia machine resulting from the higher density of xenon.[5] Thereafter, the inspired gas mixture was changed from 2 litre min^{-1} of air and 1 litre min^{-1} of oxygen to 2 litre min^{-1} of xenon and 1 litre min^{-1} of oxygen for 10 min, as described previously,[3] [6] in order to achieve an end-expiratory xenon concentration close to 1 MAC (minimum alveolar concentration) without causing hypoxaemia as a result of the expected nitrogen wash-out. For economy, the fresh gas flow was then reduced to 0.175 (SD 0.03) litre min^{-1} of xenon and 0.306 (0.02) litre min^{-1} of oxygen for the rest of the study period. End-expiratory gas, arterial and mixed-venous blood were sampled 1, 2, 3, 4, 5, 7, 10, 15, 20, 30, 60 and 120 min after starting xenon inhalation and the respective xenon concentrations were measured by gas chromatography–mass spectrometry. Whole-blood xenon calibration curves for each animal were constructed on the day of the study. The end-expiratory xenon concentration reached a plateau at 64 (6) vol% (defined as <5% change from the preceding value) after 7 min. The xenon concentrations in the arterial and mixed venous blood reached a plateau at 5 min [70 (9) μl ml^{-1} blood] and 15 min [52 (4) μl ml^{-1} blood] respectively (Fig. 1). The mixed venous xenon concentration continued to rise slowly until the end of the observation period at 120 min of xenon inhalation [63 (3) μl ml^{-1} blood]. The arterial–mixed venous (A–V) xenon concentration difference peaked at 3 min at a mean value of 34 (22) μl ml^{-1} blood, which did not significantly differ from the values at 2, 4 and 5 min. Thereafter the A–V content difference declined progressively. The mean xenon uptake, calculated according to the Fick principle, was 3708 (829) ml after 30 min and 9977 (3607) ml after 120 min of xenon anaesthesia. There were no significant changes in heart rate, arterial and central venous blood pressure, intrathoracic blood volume and cardiac output during the study period.

Comment

In a pig model, we measured the xenon concentration in blood during the wash-in phase of inhalational anaesthesia. Arterial and mixed venous blood xenon concentration increased rapidly, with a time lag of 10 min, indicating the prompt establishment of equilibrium in the vascular compartment and, hence, the main target of anaesthesia, the brain. When compared with a previous study,[4] the time needed to reach an arterial equilibrium was relatively long, probably because of the lower initial fresh gas flows used in the present investigation. Gas accumulation in the gut and adipose tissue may cause the mixed venous xenon concentration to slowly rise until the end of the experiment.[7] The calculated mean xenon uptake of approximately 4 litres after 30 min and 10 litres after 120 min of inhalational anaesthesia with xenon at end-expiratory gas concentrations close to 1 MAC in 45-kg animals confirms the prediction reported by Luttropp and co-workers for an average adult during the first 2 h of xenon administration using a minimal flow technique.[8]

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Haemodynamic effects of three doses of dihydroergotamine during spinal anaesthesia

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We performed a randomized study comparing the haemodynamic effects of three doses of the vasopressor dihydroergotamine (DHE) (5, 10 and 15 μg kg^{-1}) in 30 ASA 1 and 2 patients, aged 53–87 yr, undergoing spinal anaesthesia. Non-invasive systolic arterial pressure (SAP), heart rate and central venous pressure (CVP) were recorded continuously for 25 min. Intravenous fluids were withheld during this period. All three doses of DHE reversed the lowering effects of spinal anaesthesia on SAP and CVP ($P<0.0001$), and these effects were smooth in onset and sustained. Whereas the lowest (5 μg kg^{-1}) dose restored SAP and CVP to near prespinal values, the higher (10 and 15 μg kg^{-1}) doses resulted in above-baseline increases in SAP of 7% and in CVP of 2.7 cm H_2O ($P<0.05$). The haemodynamic profile of DHE makes it a useful agent for managing hypotension during spinal anaesthesia. A dose of 5–10 μg kg^{-1} is recommended.

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Keywords: anaesthetic techniques, regional; anaesthetic techniques, subarachnoid; anaesthesia, cardiovascular; complications, vasoconstriction; sympathetic nervous system, vasoconstrictor, dihydroergotamine

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Dihydroergotamine mesylate (DHE) (Dihydergot, Novartis, North Ryde, NSW, Australia) is a vasopressor that preferentially vasoconstricts the venous system.[1 2] Its main clinical uses are in the treatment of migraine and orthostatic hypotension. It can also be used in doses of 0.5–1.0 mg to treat hypotension during spinal anaesthesia.[3 4] However, its use as a vasopressor in managing spinal anaesthesia is not well accepted and there are major regional differences in its use and availability. There is little mention of the use of DHE as a vasopressor in the anaesthetic literature. Two groups have demonstrated its efficacy.[4 5] Its main circulatory actions are to restore central blood volume and ventricular filling by constricting the venous capacitance vessels and, to a lesser extent, to maintain peripheral resistance by vasoconstricting dilated arteries.[1 2 6]

Preliminary investigations in our department have shown that, during spinal anaesthesia, i.v. DHE has a smoother onset of action and a longer duration compared with other, more commonly used vasopressors.[7] This therapeutic profile makes DHE an attractive drug for treating hypotension during spinal anaesthesia, because the peak and trough effects seen with other vasopressors are avoided.[7 8] The objective of the present study was to define the haemodynamic profile of DHE during spinal anaesthesia and to determine a suitable i.v. dose.

Methods and results

Approval by the Clinical Research Ethics Committee of the Chinese University and written informed consent were obtained. Thirty ASA 1 or 2 (16:14) Chinese patients (28 males) with mean (range, or SD) age 71 (53–87) yr and weight 62 (11) kg, scheduled for elective urological or inguinal hernia repair surgery, were recruited. They were randomized to receive DHE 5, 10 or 15 μg kg^{-1}.

Patients were fasted overnight and premedicated with oral diazepam 5–10 mg. Haemodynamic monitoring consisted of non-invasive arterial pressure measurement at 1-min intervals, electrocardiogram, pulse oximetry and a 16-gauge central venous line in the right internal jugular vein attached to a pressure transducer. Data were measured with a Datex Engstrom AS/3 Compact Monitor (Datex-Ohmeda, Helsinki, Finland) and transferred to a laptop computer, where they were displayed and stored. After a 10-min stabilization period, baseline measurements were made. The patient was then turned to the lateral position and 3 ml of

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0.5% heavy bupivacaine (Marcain Spinal 0.5% heavy; Astra, North Ryde, NSW, Australia) was injected intrathecally. The patient was then returned to the supine position and remained undisturbed for 25 min whilst data were collected. During this period no surgery was performed and i.v. fluids were withheld. Once the onset of spinal block had been confirmed by leg weakness, the preselected dose of DHE was administered i.v. with the investigator blind to the dose. The sensory level of the block to pin-prick was determined after 25 min.

Haemodynamic data were later converted to baseline and 1-min interval data using Microsoft Excel (Windows 95). This program was used to determine the greatest recorded effect of spinal anaesthesia before DHE administration and the average effect of DHE recorded between 5 and 25 min after spinal injection. The percentage change or the numerical difference in central venous pressure (CVP) with respect to the baseline for each 1-min interval was also calculated, and was used to determine the magnitude of the effect of each dose of DHE over 5 to 25 min. Statistical analysis was performed using Statview 4.5 (SAS Institute, Cary, NC, USA). Data were compared using analysis of variance (ANOVA), the Kruskal–Wallis test or the χ^2 test as appropriate. Continuous (1-min) haemodynamic data were analysed by ANOVA for repeated measures, with Bonferroni/Dunn adjustment for *post hoc* comparisons. $P<0.05$ was considered as significant.

Groups were similar with respect to patient characteristics, sensory block and baseline haemodynamic data (Table 1), with the exception of the lowest dose (5 μg kg^{-1}) group, in which the heart rate was higher ($P=0.03$). Sensory blockade reached thoracic dermatome 6 (2–10).

The response to DHE is shown in Table 1. In no patient did SAP fall below 25% of baseline. The greatest recorded decrease after spinal injection (mean (SD)) in SAP was 8 (9)%, that in CVP was 1.1 (1.1) cm H_2O and the increase in heart rate was 11 (8)%. Intravenous DHE reversed the initial depressant effects of spinal anaesthesia. SAP increased with respect to baseline values after the 10 and 15 μg kg^{-1} doses ($P<0.0001$) but remained below baseline values after the 5 μg kg^{-1} dose ($P<0.02$). Similar changes were found in mean and diastolic arterial pressures. CVP increased above baseline values after all three doses ($P<0.0001$), the increases after the 10 and 15 μg kg^{-1} doses being greater than after the 5 μg kg^{-1} dose ($P<0.02$). Heart rate increased after spinal anaesthesia and then decreased after DHE in all three groups ($P<0.0005$).

Comment

This study shows the haemodynamic effects of i.v. DHE, unmodified by i.v. fluid administration, in healthy middle-aged and elderly patients receiving spinal anaesthesia. DHE was effective in reversing the main haemodynamic effects of spinal anaesthesia because it increased blood pressure and restored CVP and thus ventricular filling. Its effects lasted at least 25 min. A dose of 5–10 μg kg^{-1}, or 0.3–0.6 mg for our average 60-kg adult, was sufficient to restore spinal-induced decreases in blood pressure and CVP within 3 min of administration.

DHE administration has few side-effects. Excessive doses can cause nausea, vomiting and vasospasm, which could be troublesome in patients with ischaemic heart disease. However, this was a greater problem with ergotamine, the predecessor of DHE.

A number of authors have studied the pharmacokinetics[2 9] and circulatory effects of DHE[10 11] during central neural block. Stanton-Hick and colleagues, in a number of eloquent studies using whole-body scintigraphy with technetium 99m-labelled erythrocytes,[10 11] showed that epidural anaesthesia caused a redistribution of blood to denervated capacitance vessels in skeletal muscle and skin at the expense of ventricular filling, which compromised cardiac output.[11] DHE preferentially constricted these capacitance vessels, replenishing the central circulation and thus ventricular filling.[10] The significance of this replenishment

Table 1 Mean (SD) values (averaged between 5 and 25 min) of systolic arterial pressure (SAP), heart rate and central venous pressure (CVP) for each dose of DHE at baseline, after spinal anaesthesia (greatest recorded effect) and after DHE administration

	Dose of DHE (μg kg^{-1})		
	5 (*n*=10)	**10 (*n*=10)**	**15 (*n*=10)**
SAP (mm Hg)			
Baseline	142 (25)	147 (19)	138 (19)
After spinal	135 (28)	136 (16)	123 (22)
After DHE	138 (28)	157 (19)	147 (28)
Heart rate (beats min^{-1})			
Baseline	80 (11)	64 (10)	66 (12)
After spinal	92 (13)	73 (14)	69 (14)
After DHE	83 (19)	60 (10)	59 (8)
CVP (cm H_2O)			
Baseline	4.7 (2.6)	5.3 (1.9)	5.5 (2.4)
After spinal	3.5 (2.1)	3.9 (2.0)	4.8 (2.5)
After DHE	5.0 (3.5)	8.1 (3.1)	8.1 (3.4)

of the central circulation was first demonstrated by Pugh and Wyndham in 1950, when they tilted the patient's head up during spinal anaesthesia and caused a reduction in ventricular filling and cardiac output, which resulted in severe hypotension.[12] Therefore, it would seem desirable to maintain an adequate circulating volume during spinal anaesthesia, and i.v. DHE seems a particularly good drug for ensuring that this happens. Compared with data collected previously by our group during spinal anaesthesia with other vasopressors,[7 8] DHE had a slower onset of effect and longer duration of action, and this seems to be an important feature of using DHE that merits further investigation.

Previously, in a similar group of patients receiving spinal anaesthesia, we found that 60% developed hypotension requiring treatment.[13] In the present study, all three doses of DHE were highly effective in preventing severe hypotension and the CVP was maintained above baseline. To restore SAP to baseline values, a dose of 5–10 $\mu g\ kg^{-1}$ was needed. Our results showed very little difference in effect between the higher 10 and 15 $\mu g\ kg^{-1}$ doses, suggesting that DHE has an upper limit to its circulatory effects, its maximal effects being an increase in blood pressure of 5–10% and an increase in CVP of 3 cm H_2O.

However, it should be noted that we studied healthy adult patients. Whether our findings are equally applicable to elderly and infirm patients, such as those with traumatic hip fracture and who frequently require spinal anaesthesia but are at much greater risk of developing hypotension, is questionable. In such patients, large increases in ventricular filling induced by DHE could precipitate acute pulmonary oedema and DHE may not have the potency to overcome the large decreases in peripheral vascular resistance that frequently occur in this more frail group of patients.[13]

Despite the positive findings of our study, DHE has not gained wide acceptance as a vasopressor for use in spinal anaesthesia. This is difficult to explain. DHE has no serious side-effect that would discourage its use. However, the market for vasopressors has been dominated for many years by ephedrine because of its extensive use in obstetric anaesthesia,[14] and this has left little freedom for other potentially useful drugs to emerge. Also, pharmaceutical companies have tended not to promote the sales of vasopressors because their clinical use is small compared with other products, such as muscle relaxants and opioids. However, despite its well-established use, ephedrine has recently been shown to be ineffective in treating hypotension during spinal anaesthesia in both elderly and obstetric patients,[14 15] which has led to renewed interest in alternative vasopressors. Recent improvements in anaesthetic monitoring systems have made it easier to study in detail their cardiovascular effects.[7 8]

In conclusion, DHE has many features to recommend its use as a vasopressor in the treatment and prevention of hypotension during spinal anaesthesia. In particular, its action has a smooth onset and a clinically useful duration. It restores CVP, which should protect against sudden cardiovascular collapse. It can be given conveniently as a single i.v. injection, and we recommend using a dose between 5 and 10 $\mu g\ kg^{-1}$.

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Prophylactic ondansetron does not improve patient satisfaction in women using PCA after Caesarean section

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Eighty-one consenting women undergoing elective Caesarean section under spinal anaesthesia were randomly divided into two groups. In Group O patients, ondansetron 4 mg was given intravenously at the end of the surgery and 8 mg added to the morphine solution in the PCA syringe. Patients in Group P received only morphine via PCA syringe. Analgesia and nausea were measured until PCA was discontinued 24 h after the operation. Women in the two groups were similar with respect to age, duration of use of the PCA, amount of morphine used, previous history of PONV, and incidence of motion sickness and morning sickness during the current pregnancy. The number of women who complained of nausea and those needing rescue antiemetic medication was significantly less in Group O. However, there was no statistically significant difference between the two groups in the patient's perception of the control of nausea and their overall satisfaction. It was noted that PONV was more frequent among women who had significant morning sickness during early pregnancy and ondansetron was beneficial in reducing PONV in these women. Although the ondansetron reduced the incidence of PONV and the need for further antiemetic medication, this did not affect patient's satisfaction regarding their postoperative care.

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Patient-controlled analgesia (PCA) with i.v. opioids provides effective postoperative analgesia, but may be limited by nausea and vomiting (PONV). Adding droperidol (0.05–0.2 mg ml^{-1}) to morphine in the PCA syringe reduces the incidence of PONV,[1–6] but is associated with increased sedation and extrapyramidal side effects. Ondansetron, a $5HT_3$ receptor antagonist, may be preferable in the postpartum period because it lacks sedative effects that may delay bonding with the baby. Although most studies on ondansetron have shown that it reduces the incidence of PONV, some workers regard this as only a 'surrogate' endpoint.[7 8] Few investigators have examined the patient's satisfaction with their treatment of PONV, which may be regarded as the more important outcome.[7 8]

The aim of our study was to evaluate whether administering prophylactic ondansetron along with morphine via PCA decreased PONV in obstetric patients and patient satisfaction.

Methods and results

This double-blind, placebo-controlled study was approved by the local research ethics committee. Eighty-one women undergoing elective Caesarean section at term under spinal subarachnoid block were selected and gave written informed consent. The sample had 80% power to detect a halving of PONV from our baseline value of 60%, found in an earlier audit. Patients with hepatic, renal, psychiatric or neurological diseases and those with pre-eclampsia were excluded. History of PONV, motion sickness, smoking, and morning sickness were noted. Subarachnoid anaesthesia was administered using 2.5–2.8 ml of hyperbaric 0.5% bupivacaine, through a 25-G pencil-point needle. All patients received co-amoxyclav 1.2 g and oxytocin 10 units i.v. after the baby was delivered and diclofenac 100 mg p.r. at the end of the operation.

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Table 1 Severity of postoperative nausea and vomiting and patient satisfaction with their control of nausea and vomiting and their overall level of care in the two treatment groups. Values represent the most severe score recorded in the postoperative period (during PCA use) and are number (%) of occurrences or responses

	Group P (*n*=40)	Group O (*n*=41)	*P* value
Nausea and vomiting (none/mild/severe/vomited)	15/2/5/18	26 / 5 / 3 / 7	0.023
Patients with morning sickness (*n*=52):			0.005
No PONV	7 (26%)	16 (64%)	
Any PONV	20 (74%)	9 (36%)	
Patients without morning sickness (*n*=29)			0.960
No PONV	8 (62%)	10 (63%)	
Any PONV	5 (38%)	6 (37%)	
Control of nausea and vomiting:			0.258
Good	24 (60%)	30 (73%)	
Moderate	10 (25%)	9 (22%)	
Poor	6 (15%)	2 (5%)	
Overall satisfaction with care:			0.9525
Good	35 (87.5%)	35 (85%)	
Moderate	4 (10%)	5 (12%)	
Poor	1 (2.5%)	1 (3%)	

Women were randomly allocated into two groups by computer-generated random numbers in sequentially-numbered envelopes. Group P received a PCA with morphine (1 mg ml^{-1}), while Group O received ondansetron 4 mg intravenously at the end of surgery plus 8 mg added to the PCA morphine syringe (60 ml) (final ondansetron concentration 0.13 mg ml^{-1}). The PCA pump was programmed to deliver 1 ml per demand with a 3 min lockout and no background infusion. Prochlorperazine 12.5 mg i.m. was available as a rescue antiemetic to any patient who requested it.

The incidence and severity of pain, sedation, nausea and vomiting were assessed using four-point scales at 15 min intervals in the immediate recovery period and then 4 hourly until the PCA pump was discontinued. A midwife, unaware of the contents of the PCA syringe, made all postoperative assessments. Twenty-four hours later, one of the investigators assessed the patient for her perception regarding overall satisfaction with her care, control of nausea and vomiting and analgesia, using a scale of good, moderate or poor.

Data were analysed using the StatView® statistical package. Discrete variables were analysed using an unpaired *t*-test or non-parametric tests. Categorical variables were analysed using the chi squared or Fisher's exact test, as appropriate. In all cases a *P* value of <0.05 was considered significant.

Patient characteristics between the two groups were similar except that the women in Group O were slightly heavier. There were no significant differences in the amount of morphine used, history of motion sickness, morning sickness, smoking, and PONV. The incidence of intraoperative hypotension and the requirement for an infusion of oxytocin to assist postoperative uterine contraction did not differ between the groups. There were no differences in the degree of pain between the two treatment groups at any time. Most patients were either pain-free or had only mild pain. All patients were awake or arousable to voice at all times.

The incidence of nausea and vomiting was significantly lower in the ondansetron group (Table 1). Twenty-three (57%) patients in Group P experienced severe nausea or vomiting compared with 10 (24%) in Group O ($P<0.01$). Eighteen women from Group P needed rescue antiemetic, compared with only five from Group O ($P<0.01$). Ondansetron was effective in reducing the incidence of PONV in those patients who had previously experienced morning sickness but not in those who had not (Table 1). There was no differential efficacy of ondansetron in patients with and without previous PONV, smoking or motion sickness, although the number of patients with these risk factors was relatively small. Six patients in Group P and two in Group O felt that the control of nausea and vomiting was 'poor', the difference was not significant. One patient in each group felt their overall care was unsatisfactory (Table 1).

Comment

In post-Caesarean section patients, we found that adding ondansetron to morphine in the PCA syringe reduces the incidence of PONV and the requirement for antiemetic rescue without increasing sedation. However, it seemed to make little difference to the patient's perception of the control of their nausea or her feeling of satisfaction with the overall quality of care. This is consistent with other workers who reported that reducing the incidence of PONV did not improve patient satisfaction.[9]

There are various factors that may contribute to PONV.[10] The most important predictors are female gender, previous PONV, prolonged surgery, non-smoking, and motion sickness.[10] We found that the incidence of PONV was higher among women who had significant morning sickness during early pregnancy. Ondansetron was beneficial in reducing PONV in these women, but appeared to make little difference in patients who did not experience significant morning sickness.

Prophylaxis of PONV is usually administered once or intermittently. There are a few studies where the antiemetic was added into the PCA syringe.[1–6] Droperidol was used in most of these and was found to be effective, but caused increased sedation, a side effect that we felt was undesirable in the postpartum period. Postoperative sedation was rare in our patients and was not increased by the use of ondansetron. Alexander and colleagues showed that a bolus of ondansetron 4 mg plus 0.13 mg ml^{-1} in the PCA syringe was effective in reducing PONV after orthopaedic surgery.[2] This technique has not previously been investigated in postpartum patients.

When questioned about their perception of nausea and overall care, the responses of the two groups were similar, despite considerable differences in the incidence of PONV and request for rescue antiemetics. The high level of satisfaction could partly be a result of the euphoria of having a newborn baby and to the extra attention given by a sympathetic investigator who spent extra time with them. However, this should have applied equally to both groups.

Ondansetron is safe and effective, with a low incidence of adverse effects such as headache, dizziness, and increased liver enzymes. It has also been shown to be compatible with morphine sulphate.[2] There are no reports of adverse effects of ondansetron in women who are breast feeding, although the manufacturer cautions against its use in this situation. However, similar advice applies to droperidol and prochlorperazine.

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BJA

CASE REPORTS

Onset of propofol-induced burst suppression may be correctly detected as deepening of anaesthesia by approximate entropy but not by bispectral index

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The bispectral index (BIS) is a complex EEG variable that combines several disparate descriptors of the EEG into a single value. Approximate entropy is a novel EEG measure that quantifies the regularity of a data time series such as EEG. We report two patients in which the EEG effect of propofol was quantified very similarly by BIS and approximate entropy. However, at the beginning of burst suppression of the EEG, BIS did not indicate an increased anaesthetic drug effect, while approximate entropy did.

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The bispectral index (BIS, Aspect Medical Systems, Framingham, MA, USA) is a complex EEG variable that combines several disparate descriptors of the EEG into a single value, the so-called BIS value. This value has been correlated with behavioural assessments of sedation and hypnosis.[1] The BIS has been used clinically to titrate depth of anaesthesia[2] and to quantify the pharmacodynamic action of anaesthetic drugs in the laboratory setting.[3]

Approximate entropy is a novel EEG measure which quantifies the regularity of a data time series such as the EEG.[4] Approximate entropy quantifies the predictability of subsequent amplitude values of the EEG, based on the knowledge of the previous amplitude values.

We report two patients in which we measured the BIS and approximate entropy at the time of onset of burst suppression of the EEG.

Patient 1

After local Institutional Ethics Committee approval and informed consent a 28-yr-old healthy female volunteer participated in a study of the action of propofol on the EEG and respiration. Assessment including drug testing, an ECG, medical history, and physical examination showed no abnormalities. Spontaneous ventilation continued throughout, and there was no type of stimulation during the study. The EEG was recorded continuously with a bipolar montage Fp1-A1,Fp2-A2 (international 10–20 system of electrode placement), using Zipprep electrodes (Aspect). Electrode impedance was kept below 2 kΩ. EEG recordings were performed with an A-1000 EEG monitor (Version 3.22, Aspect). The raw EEG signal was filtered with a 30 Hz low-pass filter and a 0.5 Hz high-pass filter. In addition to the processed EEG variables, the raw EEG signal was sampled at 128 Hz and stored on a computer hard disk for further off line analysis (Datalogger, Aspect). Approximate entropy of the EEG was calculated off-line with the settings N=1024 (length of the epoch, i.e. 1024 EEG amplitude values per epoch), m=2 (number of previous values used for the prediction of the subsequent value) and r=0.2 * SD (filtering level) as previously described.[4] Propofol concentrations were ramped up/down to predetermined concentrations using a computer controlled infusion pump (STANPUMP). All concentrations refer to effect compartment concentrations predicted by STANPUMP based on Schnider's parameter set.[5] After having established a propofol target concentration of 3 $\mu g\ ml^{-1}$ at the time 09:17, the propofol target concentration was increased to 6 $\mu g\ ml^{-1}$ at the time 09:32 (see Fig. 1). The BIS decreased to 35, the approximate entropy decreased to 0.5. At 09:47 the propofol target

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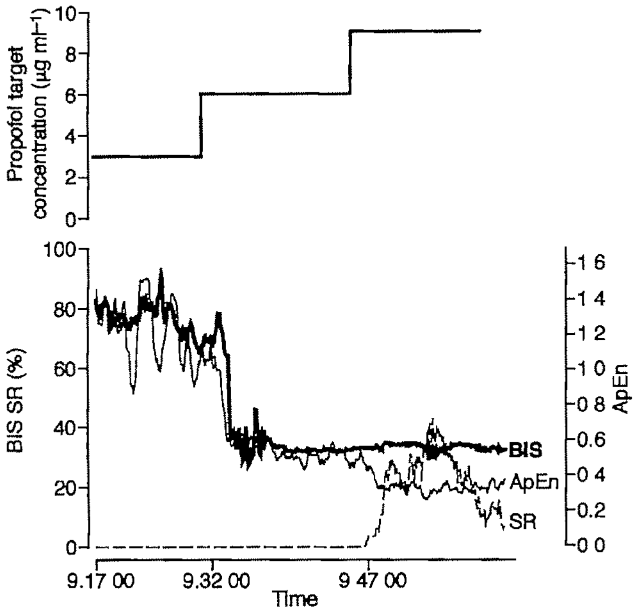

Fig 1 (Top) Propofol concentrations predicted by STANPUMP *vs* time. (Bottom) BIS (bold line), approximate entropy (ApEn, thin line), and suppression ratio (SR, dashed line) at increasing propofol target concentrations in Patient 1

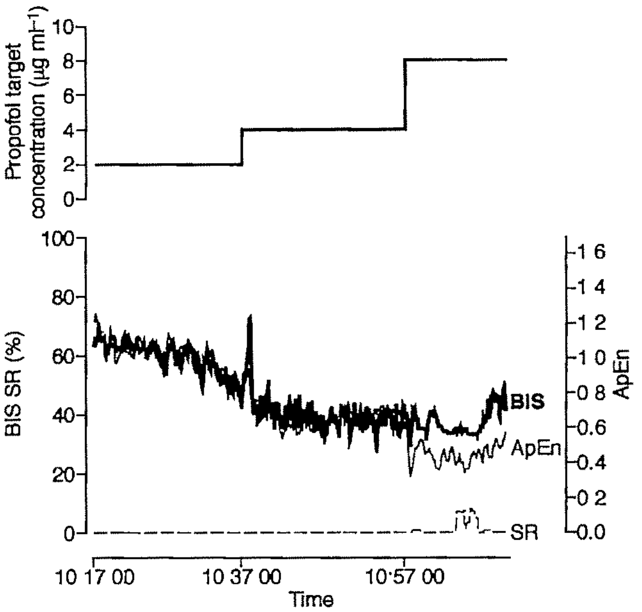

Fig 2 (Top) Propofol concentrations predicted by STANPUMP *vs* time. (Bottom) BIS (bold line), approximate entropy (ApEn, thin line) and suppression ratio (SR, dashed line) at increasing propofol target concentrations in Patient 2. From 10:17 to 10.57 BIS nearly completely parallels (i.e overlaps) approximate entropy. The abrupt and brief change of EEG parameters at 10.39 was caused by artifacts.

concentration was increased to 9 µg ml^{-1}. The BIS remained unchanged at 35, the approximate entropy further decreased to 0.35. The visual inspection of the raw EEG and the suppression ratio calculated by the Aspect monitor showed new appearance of burst suppression pattern (Fig. 1).

Patient 2

A 31-yr-old healthy female volunteer participated in the same study. The EEG montage, the EEG monitor settings and the approximate entropy calculation were the same as in Patient 1.

After having established a propofol target concentration of 2 µg ml^{-1} at the time 10:17, the propofol target concentration was increased to 4 µg ml^{-1} at the time 10:37 (see Fig. 2). The BIS decreased to 40, the approximate entropy decreased to 0.7. At 10:57, the propofol target concentration was increased to 8 µg ml^{-1}. The BIS remained unchanged at 40, the approximate entropy further decreased to 0.4. The suppression ratio calculated by the Aspect monitor showed beginning appearance of burst suppression pattern (Fig. 2).

Discussion

Between propofol target concentrations from 2 to 6 µg ml^{-1} the EEG effect of propofol was quantified very similarly by BIS and approximate entropy. This is remarkable as approximate entropy is a relatively simple single value derived from the time domain, while BIS is a complex index of several variables, requiring third order statistics.[1] As this concentration range covers the clinically relevant range (with co-administration of opioid), the BIS adequately reflects EEG changes in the therapeutic range of propofol.

The higher variations of the approximate entropy values compared with the BIS values at low propofol target concentrations in Patient 1 are because approximate entropy is calculated without artifact rejection, while an artifact rejection mode is incorporated in the BIS algorithm.

In the first patient, burst suppression appeared after increasing propofol target concentration from 6 to 9 µg ml^{-1}. Although, burst suppression ratio is a part of the BIS algorithm,[1 6] this did not change the BIS. As the suppression part of the burst suppression pattern is classified as highly regular, the approximate entropy algorithm correctly classifies increasing burst suppression ratio as increasing anaesthetic drug effect.[7] The decrease of approximate entropy indicated the increased pharmacodynamic action.

In the second patient, the BIS remained unchanged despite an increase of the propofol target concentration from 4 to 8 µg ml^{-1}. The suppression ratio calculated by the Aspect monitor (Fig. 2) failed to indicate additional CNS suppression. The change in approximate entropy value indicated the pharmacodynamic situation. At this time, quantification of the phase coupling by the BIS appeared less sensitive to drug effect than quantification of regularity by approximate entropy.

With an older BIS version (version 3.12) and a combination of sufentanil, nitrous oxide, and isoflurane Detsch and colleagues recently reported paradoxical increases of BIS when isoflurane concentrations was increased.[8] This was noted in the same range of BIS values between 30 and 40, where we found that the more recent BIS version (version 3.22) gave a value of BIS that failed to indicate increased propofol effect.

BIS values between 40 and 60 have been suggested as clinically adequate during surgery. The range of uncertainty between phase coupling and burst suppression ratio is at BIS values between 30 and 40. Targeting BIS between 40 and 60, a BIS value between 30 and 40 is always a 'too deep' state of anaesthesia. The cases we report demonstrate that, based on the BIS alone, it may be difficult to determine how much 'too deep' the state of anaesthesia is, which is clinically relevant information. Choosing the suppression ratio as a second trend line on the Aspect monitor, or visual inspection of the raw EEG on the screen for burst suppression pattern would have been helpful to provide a more exact 'depth of anaesthesia' at a BIS value between 30 and 40, particularly in the first patient.

We only noted this problem with the BIS with these specific degrees of propofol drug effect at the onset of burst suppression.

When BIS values are between 30 and 40, an increased drug pharmacodynamic effect may not be adequately reflected by the BIS value. The calculation of the burst suppression ratio may be helpful, as new evidence of burst suppression or an increasing burst suppresion ratio with unchanged BIS can highlight this problem.

Approximate entropy, a measure sensitive to signal regularity, indicated EEG changes after the occurrence of burst suppression more readily than the BIS.

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Hydrothorax: an unexpected complication after laparoscopic myomectomy

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We report a case of hydrothorax as a complication of laparoscopic myomectomy in an otherwise healthy woman. The most likely cause of the patient's hydrothorax was irrigation fluid moving from the peritoneal cavity into the pleural space via defects in the diaphragm. Anaesthestists and surgeons should consider hydrothorax as a potential complication in any patient undergoing laparoscopy.

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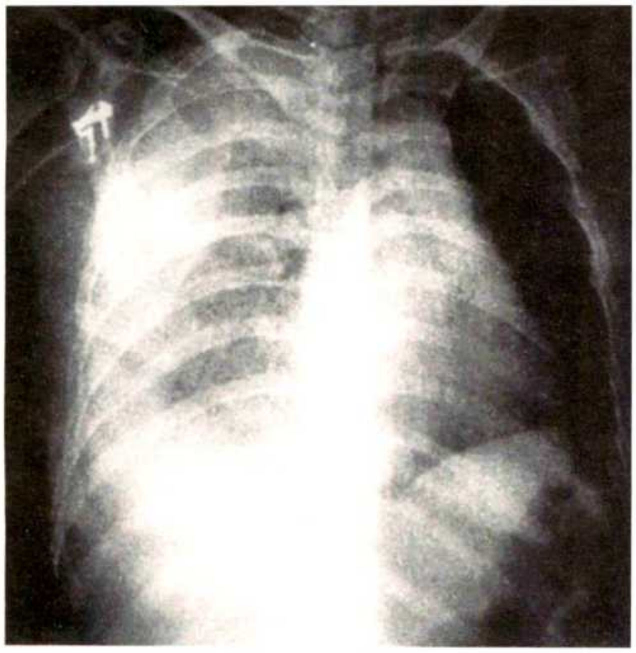

Fig 1 A chest radiograph of the patient after surgery, showing a massive right-sided pleural effusion with displacement of the mediastinum to the left.

Laparoscopic surgery is a common form of surgical therapy for many disorders. Although surgery using laparoscopy reduces morbidity and shortens recovery after surgery, laparoscopic surgery can cause unique problems. We present a patient who suffered from severe hypoxaemia after a laparoscopic myomectomy, caused by hydrothorax.

Case report

A 38-yr-old woman, weighing 52 kg and 148 cm tall, with a history of primary infertility was planned to have laparoscopic myomectomy. Pre-operative investigations were unremarkable.

Anaesthesia was induced with propofol and vecuronium, and the trachea intubated with an 8.0 mm tracheal tube. Anaesthesia was with nitrous oxide (66%), sevoflurane (1–2%), and fentanyl.

The patient was placed in the lithotomy position with slight Trendelenburg tilt. The peritoneal cavity was inflated with carbon dioxide to a pressure of 8–10 cm H_2O. Peak inspiratory airway pressure increased from 15 to 22 cm H_2O during laparoscopy. One hour after surgery began, the patient's haemoglobin oxygen saturation (Sp_{O_2}) decreased from 99 to 94%. As breath sounds were clear bilaterally, the FI_{O_2} was increased to 0.5, and the Sp_{O_2} increased to 99%. At the time that the patient became hypoxic, 2000 ml of saline had been used to irrigate the peritoneum, 1300 ml had been recovered. The remainder of the operative course was uneventful. A total of 6000 ml of saline was used for irrigation, and 5300 ml was recovered.

Four myomas were removed in a procedure that lasted for 4.5 h. The estimated blood loss was 150–200 ml. Fifteen minutes after the end of surgery, the patient was extubated and her Sp_{O_2} was 100% while breathing oxygen 6 litre min^{-1} from a face mask.

Ten minutes after extubation, the patient was moved to the post-anaesthesia care unit (PACU), while spontaneously breathing room air. On arrival in the PACU, she denied dyspnoea, but her Sp_{O_2} was only 75% while breathing oxygen 6 litre min^{-1} from a face mask. The oxygen flow was increased to 10 litre min^{-1}. Arterial blood gas analysis showed a pH of 7.38, a carbon dioxide tension (Pa_{CO_2}) of 44 mm Hg, and an oxygen tension (Pa_{O_2}) of 50 mm Hg. On auscultation, breath sounds were present but diminished over the entire right side of the chest. A chest radiograph showed a massive right-sided pleural effusion with displacement of the mediastinum to the left (Fig. 1). A chest tube was placed into the right side of the chest, and 850 ml of clear fluid was drained. The drained fluid had a sodium concentration of 149 mEq $litre^{-1}$, a potassium concentration of 2.8 mEq $litre^{-1}$ and a chloride concentration of 138 mEq $litre^{-1}$. After drainage, arterial blood gas analysis showed pH 7.38, Pa_{CO_2} of 42.9 mm Hg, and Pa_{O_2} of 123.3 mm Hg. Follow-up chest radiograph showed no hydrothorax, a midline mediastinum, and re-expansion of the right lung. The chest tube was removed 42 h after placement. The patient was discharged from the hospital 5 days after the operation.

Discussion

We describe hydrothorax as a complication of laparoscopic surgery in an otherwise healthy woman. Fortunately, she recovered uneventfully with standard treatment. The most likely cause of the patient's hydrothorax is the passage of a large volume of irrigation fluid from the peritoneal cavity into the pleural space via defects in the diaphragm. This theory is supported by the evidence that the electrolyte concentrations of the drained fluid (Na 149 mEq $litre^{-1}$, Cl 138 mEq $litre^{-1}$) which were almost identical to that of the saline, which was used as irrigant solution. During surgery, 6000 ml of saline was used for irrigation. The recovery irrigation was in a negative balance throughout surgery. Although theatre irrigation balances are often inaccurate, we suspect that this volume drained into the pleural cavity. The chest radiograph clearly demonstrated a large hydrothorax, and 850 ml of fluid was drained. The fact that the patient was small probably explains the marked x-ray findings. The surgery took a long time (4.5 h), because four myomas were removed. This may have affected the development of the hydrothorax as the patient was in Trendelenburg position during the course of operation.

One hour after beginning of the operation, the Sp_{O_2} decreased to 94%. At this time, pleural fluid may have already accumulated because the irrigation fluid balance was –700 ml. However, the effect of the effusion on Sp_{O_2}

may have been overcome by the increase in $F\mathrm{I}_{\mathrm{O}_2}$, which improved the Sp_{O_2} to 99%. Throughout surgery, intermittent positive pressure ventilation may have prevented further collapse of the lung. A high $F\mathrm{I}_{\mathrm{O}_2}$ prevented a decrease in Sp_{O_2} immediately upon extubation. Breathing room air during the transportation to the PACU showed the pathology.

Possible channels of communication between the peritoneal cavity and the pleural cavity have been reported. They can be collectively and comprehensively regarded as porous diaphragm syndrome.[1] Hydrothorax complicating abdominal ascites and peritoneal dialysis has been reported. Hepatic hydrothorax is defined as a pleural effusion in a patient with liver cirrhosis and no cardiopulmonary disease.[2,3] Recent studies have confirmed that small defects in the diaphragm allow for passage of ascitic fluid into the pleural space.[1,4] A defect in the diaphragm in a patient with cirrhosis and hydrothorax was first described in 1955 and proposed as a cause of hepatic hydrothorax.[2] These diaphragm defects can be demonstrated both grossly and microscopically.[5,6] Hepatic hydrothorax is usually right-sided (85%).[3] Hydrothorax complicating peritoneal dialysis is also well documented,[7–9] also more commonly on the right.[9] Congenital or acquired defects in the diaphragm[8] allow the dialysate to reach the pleural space. Hydrothorax in dialysis patients may appear during the first dialysis treatment, or may be delayed and not appear until after months or even years of dialysis.[9] This bimodal incidence pattern, also seen when artificial pneumoperitoneum leads to pneumothorax, suggests that the diaphragmatic defect may be either congenital or acquired.[1]

Gallagher and colleagues described a case of tension hydrothorax after hysteroscopy complicated by occult uterine rupture.[10] McConnell and colleagues reported tension hydrothorax during laparoscopy in a patient with ascites and pleural effusions;[11] who may have already had a patent pathway for the movement of ascites into the pleural space.

Congenital (pre-existing) defects are probably less prevalent than acquire defects. Hydrothorax is found in liver cirrhosis and peritoneal dialysis with prevalences of 6% (range, 0.4–12.2%) and 2% respectively.[1,4,9] If we assume that these incidences are representative of the percentage of the general population who have peritoneothoracic communications, then a substantial number of patients are at risk for developing hydrothorax or pneumothorax after laparoscopic surgery. It is important for anaesthesiologists and surgeons to recognize hydrothorax as a potential complication in any patient undergoing laparoscopy especially when a negative irrigation balance is identified.

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Transient right phrenic nerve palsy associated with central venous catheterization

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An 85-yr-old woman with advanced sigmoid colon cancer developed right phrenic nerve palsy following central venous catheterization for preoperative nutritional and fluid balance improvement. The central venous catheter was successfully placed via the left subclavian vein at the first attempt. Blood returned freely through the catheter. The chest x-ray film taken immediately after the catheterization showed the proper placement of the catheter, but it revealed a significant right hemidiaphragmatic elevation indicating phrenic nerve palsy. A chest computed tomography scan and bronchoscopy were normal. As the patient did not complain of dyspnoea and vital signs were normal, tumour resection was performed. The operative and postoperative course was uneventful. The chest x-ray film after the surgery still showed the elevation of the right hemidiaphragm. It resolved completely within 3 days of withdrawing the central venous catheter by 3 cm on the fourth postoperative day. We concluded the likely cause of the phrenic nerve palsy was that the catheter tip impinged upon the thin venous wall and compressed the phrenic nerve running alongside the superior vena cava.

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Keywords: equipment, central venous catheter; complications, hemidiaphragmatic elevation; complications, phrenic nerve palsy

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Phrenic nerve palsy has been reported as one of the possible complications of central venous catheterization. Although the incidence of this is rare, it may worsen the respiratory function of patients who have been compromised under pulmonary illness. We present a case in which a patient developed right phrenic nerve palsy after central venous catheterization, the cause of which was most likely the compression of the phrenic nerve, running alongside the superior vena cava, by the impinged catheter tip upon the wall of the vein.

Case report

An 85-yr-old woman with advanced sigmoid colon cancer was admitted to hospital as an emergency because of increasing abdominal distension. The plain x-ray film showed distended large bowel with gas, suggesting a deterioration of bowel obstruction. A rectal tube was raised beyond the obstruction site into the descending colon under fluoroscopy to lessen the abdominal distension. The chest x-ray film was normal.

On the third day of admission, central venous catheterization was attempted to improve the nutritional and fluid balance of the patient before surgery. A 16-G catheter was passed into the left subclavian vein through an infraclavicular approach at the first attempt. Blood returned freely through the catheter. The chest x-ray film confirmed the proper placement of the catheter, but it also showed an elevation of the right side hemidiaphragm (Fig. 1). The patient was not dyspnoeic and the arterial blood gas data were normal.

A chest computed tomography scan (CT) revealed a single metastatsic nodule in the lower lobe of the right lung and a small amount of pleural effusion in the right hemithorax. Neither the chest CT scan nor subsequent bronchoscopic examination demonstrated any other abnormaity that might explain the right hemidiaphragmatic elevation.

On the 18th day of admission, resection of the sigmoid colon with formation of a colostomy was performed under general anaesthesia. In spite of the persistent elevation of the right hemidiaphragm, the patient's postoperative recov-

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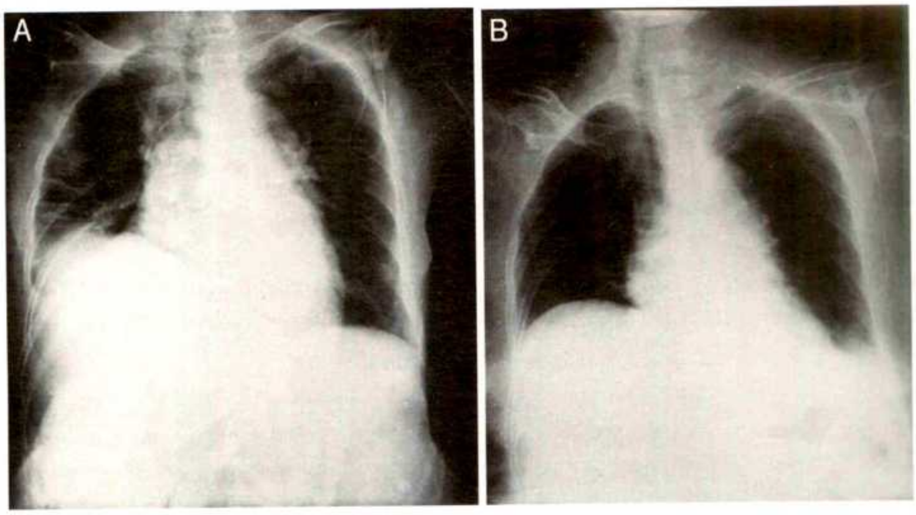

Fig 1 (A) On the left side, supine chest film immediately after inserting the central venous catheter via the subclavian vein, showing the proper placement of the catheter and the right hemidiaphragmatic elevation. (B) On the right side, supine chest film 3 days after withdrawing the catheter, demonstrating the complete restoration of the right hemidiaphragm.

ery was uneventful. On the fourth postoperative day, the tip of the catheter was withdrawn by 3 cm because the flow rate of infusion fluid through the catheter was sluggish and the chest X-ray film showed the catheter tip to be impinged more perpendicularly on the wall of the superior vena cava than in the previous films. The infusion speed improved and the chest x-ray film 3 days after the withdrawal revealed complete resolution of the right phrenic nerve palsy (Fig. 1). On the 17th postoperative day the patient was discharged from hospital with no recurrence of the phrenic nerve palsy.

Discussion

Phrenic nerve palsy related to central venous catheterization is uncommon. There have been several reports, and various causes proposed. Direct nerve injury as a result of repeated venipuncuture at the internal jugular vein while siting the catheter;[1,2] haematoma produced by an inadvertent arterial puncture during catheterization of the right subclavian vein;[3] lidocaine instillation before right internal jugular vein catheterization;[4] and nerve compression from the inflamed venous wall adjacent to the phrenic nerve 55 days after catheterization.[5]

In our case we punctured the left subclavian vein by the infraclavicular approach where there is no possibility of damaging the right phrenic nerve with the needle, local anaesthetic infiltration and/or haematoma formation at the puncture site. One possible cause for the right phrenic nerve damage was the compression of the nerve through the vein wall by the tip of the catheter. When a central venous catheter is introduced through the left subclavian vein, the tip of the catheter hits the wall of the superior vena cava more perpendicularly than when it is introduced from the right side. Central venous catheter-related vascular erosion or perforation is more common when the catheter is introduced from the left subclavian vein.[6,7] Therefore, we concluded that the cause of the phrenic nerve palsy was the tip of relatively rigid polyurethane catheter impinging upon the thin venous wall and compressing the phrenic nerve running alongside the superior vena cava.

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Spinal cord injury caused by direct damage by local anaesthetic infiltration needle

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We describe a case of spinal cord injury caused by direct trauma from a local anaesthetic infiltration needle. During local anaesthetic infiltration before placement of an epidural catheter, the patient suddenly rolled over onto her back, causing the infiltrating needle to advance all the way to its hub. She immediately showed signs of spinal cord injury, confirmed by MRI scan. However, her neurological status gradually improved, and on discharge she was able to walk, with a sensory deficit localized to her left foot.

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In recent years, the anaesthetic literature has contained much discussion about the safety of performing epidural anaesthesia in unconscious patients. Bromage[1] and Wildsmith[2] argue against the performance of central neural blockade in anaesthetized patients. In Germany, after a report of two cases of traumatic cord injury arising during thoracic epidurals performed under general anaesthesia,[3] national guidelines were published stating that prior general anaesthesia is an absolute contraindication to thoracic epidural blockade and a relative contraindication to all other central neural blocks. Nonetheless, there is no general consensus on the subject. Fischer maintains that not only is the practice of anaesthetizing patients before regional blockade widespread in the UK and elsewhere, but also that there are insufficient data to show that the risks of regional anaesthesia are increased in unconscious patients.[4]

It is often unwise to have absolute rules in medical practice, as cases should be judged according to their specific circumstances. This is illustrated by the case reported here, in which a spinal cord injury that occurred during insertion of an epidural catheter might have been avoided if the procedure had been performed after induction of anaesthesia.

Case history

A 31-yr-old woman (height 157 cm, weight 50 kg) presented with a history of intermittent small bowel obstruction. She had had a tubal ectopic pregnancy 1 yr previously. On laparotomy, she was found to have tuberculous salpingitis. This responded initially to conventional anti-tuberculous chemotherapy. Before this admission, she had developed subacute distal ileal obstruction secondary to adhesions caused by the salpingitis. Ultrasound and a CT scan confirmed this, and she was prepared for urgent laparotomy under combined general anaesthesia and epidural analgesia.

She was extremely nervous, and did not speak English. According to her religion, she could only speak via her husband or brother to an interpreter, who then spoke to the anaesthetist (N.B.S.). Premedication was avoided so as not to interfere with communication during insertion of the epidural. The instructions were repeated to her through her husband, and in particular she was asked to remain as still as possible. Midazolam 3 mg was then administered i.v. This caused her to become somewhat disinhibited, but the anaesthetist was loath to administer a further dose and risk oversedation. At the pre-operative visit, the patient and her husband were adamant that the anaesthetist should do whatever was necessary to ensure that she had no pain after the operation. Thus, it was decided to continue with the procedure. She was placed in the left lateral position and the skin in the low thoracic and upper lumbar region was prepared and draped. She was not ‘stabilized’ or restrained by a member of staff.

At the T11/12 interspace, 3 ml of 2% lignocaine was injected via a 21 G needle (Microlance 3, Becton Dickinson, Oxford, UK; length 4 cm) for local anaesthesia. During subcutaneous infiltration the patient suddenly flung her arms out, and then rolled towards the anaesthetist onto her back,

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causing the infiltrating needle to be advanced to its hub and trapping the hands of the anaesthetist. The patient felt a shock-like sensation, running from the site of insertion of the needle down both legs, but worse on the left. After the needle was withdrawn, she complained of a transient sharp pain all over the body and then heaviness, numbness, and paraesthesia in the left leg down to the foot. On examination she could not bend her left knee. Initially, it was thought that a small amount of the local anaesthetic might have been injected intrathecally. However, the clinical findings did not progress over the next 10–15 min. After discussion with the gynaecologist and general surgeon, surgery was postponed and an urgent MRI scan was arranged. This revealed a focal signal void in the dorsal epidural space opposite T11/12, consistent with a small volume of air having been injected into the epidural space. It also showed an area of spinal cord oedema at the same level, consistent with a needle-stick injury.

The following day there was no change in the clinical picture. Micturition and defaecation were normal but she complained of dizziness and backache on mobilization. Forty-eight hours later, she developed septicaemia and disseminated intravascular coagulation (DIC) requiring admission to the intensive care unit (ICU). Her condition responded to fluid resuscitation, dopamine, i.v. antibiotics, clotting factors and platelets. After a further 48 h, she underwent laparotomy under general anaesthesia. Findings at laparotomy were polycystic ovarian disease, tubo-ovarian abscess, and multiple adhesions in the pelvis with adherent loops of small bowel. Bilateral salpingo-oophorectomy and division of adhesions were performed. After surgery, the sepsis and DIC persisted for a further 4 days and she remained in the ICU during this period. She then made a rapid and full recovery from the operation.

Neurological recovery was slow but progressive and was assessed regularly by a consultant neurologist. From his initial assessment he was confident of complete eventual recovery. A second MRI, performed 14 days after the needle-stick injury, demonstrated disappearance of low-signal material in the epidural space dorsal to the conus region of the spinal cord, compatible with resorption of air from the epidural space. There was a focal area of high signal in the conus suggestive of cord oedema or myelomalacia.

Eighteen days after the needle-stick injury, her balance and ability to walk had recovered almost fully. The heaviness of the left leg had improved, as had the paraesthesia, which had become localized to the sole of the left foot. Temperature and touch sensation were normal. She still had some pain in the lumbar region but not at the site of injection. Anal and bladder sphincter function remained normal throughout. Clinical examination revealed a slight weakness in the left leg but, after a further 7 days, she was able to take a few steps on her tiptoes. Heel–shin coordination was normal on both sides. Reflexes were equal on both sides, but the left plantar response was extensor. Temperature sensation was intact. Light touch sensation was reduced in the sole and the lateral border of the left foot. Pinprick sensation was blunted from L3 caudad.

She was discharged home soon afterwards, but repeated attempts to contact her since then have failed.

Discussion

Regional anaesthesia has many benefits. When used alone or combined with general anaesthesia for major surgery, it has been shown to reduce post-operative mortality and the incidence of several other complications, such as deep vein thromboses, pulmonary embolism, stroke, myocardial infarction, wound infection and pneumonia.[5]

However, the benefits of regional anaesthesia must be balanced with the risks, the most serious of which are neurological injury. Fortunately, several large studies of the complications of regional anaesthesia have confirmed that neurological injuries are rare, and are usually injuries to a single spinal nerve. In the 1950s[6] and 1960s,[7] large prospective studies of the complications of spinal anaesthesia were performed. Each of these two studies involved more than 10 000 cases, and neither found any cases of arachnoiditis, cauda equina syndrome or transverse myelitis. However, the later study did identify 38 patients with peripheral nerve symptoms—transient in 30 cases and permanent in eight. Similarly, the former study identified 17 patients in whom traumatic lumbar puncture was associated with transient peripheral neurological symptoms.

The results from recent studies are similar.[8–10] Scott and Hibbard reviewed 500 000 obstetric patients who received extradural anaesthesia.[9] Of these, there was one case of permanent neuropathy, a case of quadriplegia due to thrombosis of a cervical haemangioma, and a case of paraplegia, probably due to anterior spinal artery syndrome. In a prospective study of more than 100 000 spinal and epidural anaesthetics, there was one case of paraplegia after combined spinal–epidural anaesthesia, presumed to be due to spinal ischaemia, and five cases of cauda equina syndrome.[10] In a study of 18 000 consecutive central blocks in Sweden, there were three cases of paraplegia caused by spinal haematomas in patients with coagulopathy.[8] Other serious but rare complications include cardiac arrest and seizures.[10]

Although none of these large studies identified any cases of direct traumatic spinal cord injury caused by a spinal or epidural needle, in recent years there have been several case reports of such injuries. Cases have been reported of lower limb paresis due to spinal cord injury caused by a spinal needle[11 12] and of serious spinal cord injuries sustained during attempted epidural anaesthesia, confirmed by MRI, at operation or at post-mortem.[13–15] In one case,[13] the epidural catheter and possibly the epidural needle entered the cord. As far as we are aware, ours is the first reported case of spinal cord injury caused by a hypodermic needle used for local anaesthetic infiltration.

The authors of these reports tend to support the views of Bromage[1] and Wildsmith[2] that regional blockade is best performed in conscious patients. The main argument is that unconscious subjects are unable to report paraesthesia, a sign warning of the proximity of a needle or catheter to the cord. This sign was present in all the reports of spinal cord injury in awake patients.[11–13 15]

While we believe that regional anaesthesia is safest when performed in awake patients, in this particular case the spinal cord damage might have been avoided if the epidural had been performed after the patient was anaesthetized. If this had been done, one option would have been to insert the epidural catheter in the lumbar epidural space, below the level of the cord. However, the disadvantages of increased loss of motor function and delayed mobilization were felt to outweigh the benefit of a potential reduction in risk of spinal cord injury.

Unfortunately, there were many factors making it difficult for our patient to cooperate. She did not receive a sedative premedication and arrived in the postanaesthesia care unit in an anxious state. There were communication difficulties, and it is likely that she found the hospital and theatre intimidating and frightening. As she and her husband had demanded a pain-free recovery, the option of abandoning the epidural anaesthetic at this stage was not considered appropriate. Had she been restrained, the neurological injury might have been avoided, but this practice is not considered acceptable in the UK.

Several of the reported cases of direct cord injury occurred in patients in whom the epidural space was difficult to locate, and so occurred during the course of failed spinal or epidural anaesthesia.[12 14 15] The patient in our report was slim, with easily identifiable landmarks and an epidural space that was likely to be easy to locate. It is thus unlikely that difficulties would have arisen if the procedure had been performed while she was unconscious.

In our patient, the 4-cm infiltrating needle was able to penetrate the skin, ligaments and epidural and subarachnoid spaces into the cord. In the majority of patients the distance from the skin to the epidural space is between 4 and 6 cm. However, in thin patients this distance can be <3 cm.[16] In the lumbar region there is a 1 in 6 chance of encountering the epidural space between 2 and 4 cm,[17] and one can expect to encounter the subarachnoid membrane after a further 4–7 mm.[18] In slim patients, it may thus be wiser to infiltrate local anaesthetic agents through shorter needles to reduce the risk of inadvertent dural puncture and spinal cord injury.

As always, the importance of clear communication and careful explanation of all invasive procedures to patients and their relatives cannot be over-stressed, as better understanding usually leads to improved cooperation. In the UK, while the culturally entrenched expectation persists that all unpleasant procedures should be performed under general anaesthesia, there will always be patients who, after being informed of the benefits of regional anaesthesia, prefer to have this performed whilst asleep. If rigid guidelines are introduced, preventing epidural blockade in the unconscious, then these patients may not receive the benefits of regional anaesthesia and analgesia, for the sake of an unproven reduction in the risk of spinal cord injury (a risk that, though potentially catastrophic, is very small). Thus, while national guidelines such as those introduced in Germany are laudable, they should be thought out carefully and there should be room for flexibility, so that each case can be judged on its own merits.

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British Journal of Anaesthesia **87** (**3**): 515–17 (2001)

Tracheobronchopathia osteoplastica: incidental finding at tracheal intubation

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Subglottic papillomatous growths were observed on routine tracheal intubation for a scheduled colorectal procedure. Fibreoptic bronchoscopy revealed that the lesions extended down to the carina and into the main bronchi. The diagnosis of tracheobronchopathia osteoplastica was made after subsequent bronchoscopy and biopsy in the post-operative period. A brief review of this rare benign condition is given.

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Keywords: lung, tracheobronchopathia osteoplastica; complications, tracheal intubation

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An 83-yr-old man presented for elective surgery for carcinoma of the sigmoid colon. Six months earlier he had had an uneventful inguinal hernia repair, which was performed as a day case under general anaesthesia. The patient had been allowed to breathe spontaneously through a laryngeal mask on that occasion. Apart from a history of trigeminal nerve neuralgia and duodenal ulceration, he was fit.

On the day of surgery, anaesthesia was induced with propofol 200 mg and fentanyl 100 µg, and muscle relaxation was achieved with vecuronium 8 mg. Oxygen saturation when breathing air was 96%. After induction of anaesthesia, the patient was haemodynamically stable and oxygen saturation was 98% when he was ventilated with 50% oxygen in nitrous oxide. On laryngoscopy, the larynx was easily visualized, but when a size 9.0 cuffed tracheal tube was passed through the cords subglottic resistance was encountered. The tube was removed and on further laryngoscopy a small nodular growth was seen on the anterior aspect of the trachea in the immediate subglottic region. An opinion was obtained from a consultant ENT surgeon in an adjacent operating theatre, who was uncertain about the diagnosis, but stated that the growth looked benign. As the patient had no respiratory symptoms, it was decided, after discussion with the surgical team, to proceed with surgery.

A size 8.0 cuffed tracheal tube was passed easily, and before surgery was begun fibre-optic bronchoscopy was performed through the tracheal tube. This revealed superficial nodular lesions, which spread down the trachea to the carina and into the main bronchi. A photograph was taken of the lesions (Fig. 1), but a biopsy was not attempted in order to prevent unwanted bleeding into the bronchial tree.

An uneventful sigmoid colectomy was performed and, apart from partial left lower lobe collapse, which responded to physiotherapy, the post-operative period was unremarkable.

After he had recovered from surgery, the patient was referred to the respiratory physicians. Bronchoscopy was performed and a biopsy of the lesions was taken with some difficulty because of their bony nature. A photograph taken of the subglottic region of the trachea (Fig. 2) shows the extent of the lesions.

Histology reported a diagnosis of tracheobronchopathia osteoplastica. The patient was discharged with a follow-up appointment for the chest clinic.

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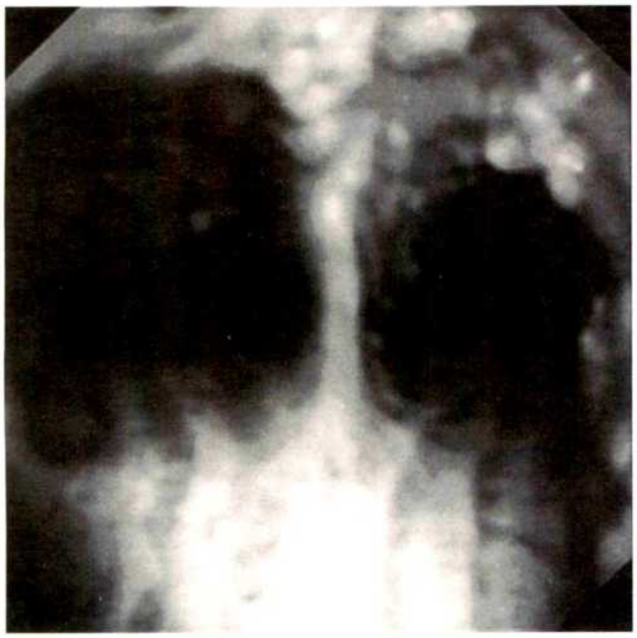

Fig 1 Bronchoscopic view of carina and main bronchi before surgery.

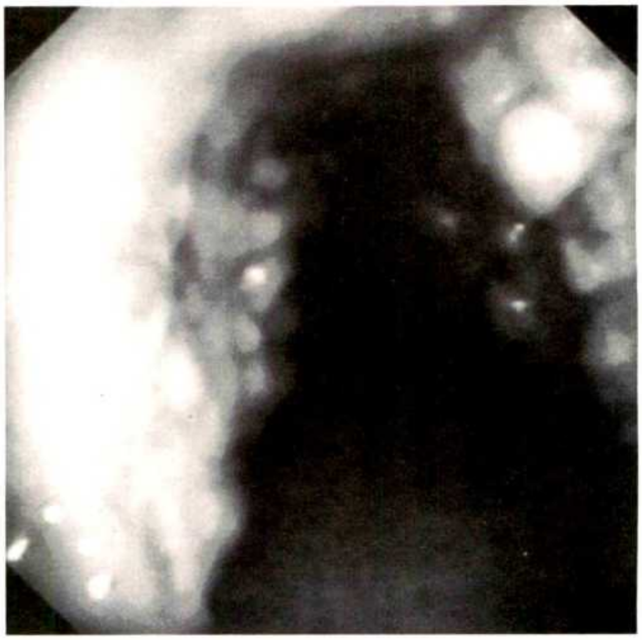

Fig 2 Bronchoscopic view of subglottic region when a biopsy was taken of numerous nodules on the anterior aspect of the trachea. Note the 'cobblestone' or 'rock garden' appearance.[11]

Discussion

Tracheobronchopathia osteochondroplastica is a rare, benign condition and is characterized by the presence of bony and cartilaginous nodules in the tracheal and bronchial mucosa. It was first described by Wilks, physician to Guy's Hospital, in 1857 in a 38-yr-old man who died of tuberculosis. At autopsy, he found the larynx, trachea and bronchi to be 'covered with a number of bony plates'.[1] He also noted that these bony deposits were predominantly anterior to the trachea and lay between the cartilaginous rings.

The cause of the condition is unknown, but several theories have been postulated. Ecchondroses and endochondroses from the tracheal rings were first suggested by Virchow in 1863.[2] In 1910, Aschoff[3] suggested that metaplasia of the elastic tissue may be the cause. More recently, Sakula[4] put forward the theory that tracheobronchopathia might be a form of primary localized amyloidosis of the lower respiratory tract that has undergone ossification. However, histology findings do not support this suggestion. A possible association with atrophic rhinitis and pharyngitis was found by Harma and Suurkari,[5] who suggested that the lesions were due to a build-up of calcium salts within the tracheal mucosa that led to the development of local bony nodules.

The case we describe is consistent with the classical presentation of normal mucosa covering bony or cartilaginous nodules on the tracheal walls, the membranous posterior portion of the trachea usually being spared (Fig. 2). The lesions most commonly occur in the lower two-thirds of the trachea but may extend anywhere from the larynx to the bronchi.[6] Histological findings are typically of bony and cartilaginous nodules (some even demonstrating haemopoiesis) situated in the submucosa, invariably with connections of bone, cartilage or connective tissue to the perichondrium of the tracheal rings.[7]

Most cases are asymptomatic, so it is difficult to estimate the incidence of the disease accurately. Pounder and Pieterse[8] reported the incidental finding at autopsy to be as high as 1 in 400. Primer[9] reported the disease, again as an incidental finding, in four out of 550 bronchoscopies. Males and females are equally affected and age at the time of diagnosis is usually above 50 yr,[10] although some cases have been reported in young adults and children.[5] Those who do present with symptoms typically complain of progressive dyspnoea associated with a chronic cough. This may be associated with intermittent hoarseness, the production of blood-streaked crusts and repeated chest infections.[10]

Diagnosis is confirmed by bronchoscopy and the lesions have been described as having the appearance of cobblestones or a rock garden[11] (Fig. 2). Radiological diagnosis on plain chest X-ray is rare, but computed tomography of the neck has detected even very mild cases[12] Functional alterations induced by the lesions are variable and depend upon the severity of the disease and the site of the lesion. Spirometry is often normal, but patients with more extensive disease show a mainly obstructive pattern.[13 14]

Only two cases have been described of tracheobronchopathia osteoplastica as a cause of unexpected difficult intubation due to subglottic obstruction.[10 15] In both cases, the disease was extensive and caused significant problems with intubation. One of the cases was so severe[10] that a size 4.0 microlaryngoscopy tube was eventually passed over a bougie that had been placed through a rigid bronchoscope. In this case, the lesion was removed with a carbon dioxide laser before the patient was extubated the following day.

If this rare condition is discovered at intubation, the extent of the disease and the urgency of surgery affect the decision about whether to continue the operation. It was fortuitous that we had an ENT opinion immediately available, and although the lesion was widespread it was superficial and the obstructive component was minimal. Had the surgery been less urgent, we would not have proceeded but referred the patient to an appropriate specialist.

Most cases of tracheobronchopathia osteoplastica are asymptomatic and the prognosis is generally good. In our literature search, the case described by Birzgalis[10] is the only record of the disease requiring surgical intervention.

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Cognitive decline following cardiac surgery

Editor—In a recent paper, Millar and colleagues[1] propose that the risk of cognitive decline following cardiac surgery is increased in individuals who show evidence of cognitive impairment preoperatively. While this hypothesis is provocative, we believe that such a conclusion is limited by two aspects First, the claim that normative data for the Stroop test 'allow an individual's score to be categorized as indicative of likely brain damage as a function of their age' (p 64) is incorrect. Brain damage can never be determined solely on the basis of one or even many neuropsychological tests. Even if poor performance is interpreted more cautiously as reflecting a cognitive deficit, it is well-known that performance on the Stroop task is related to both age and intelligence in the general population.[2] It is possible, therefore, that individuals who showed poor performance on the Stroop test preoperatively and were thus categorized as 'impaired', were those who were older or who had a lower premorbid IQ. In fact, the regression analysis conducted on the entire group shows that, together, age and estimated premorbid IQ, accounted for 34% of the variance in Stroop test performance at the 6-day assessment and 24% of the variance at the 6-month assessment.

Second, we believe that the use of a binary classification for cognitive impairment reduced the power of the study to detect true postoperative cognitive decline. For example, each patient's performance on the three repeated assessments with the Stroop test was compared to the normative data derived from a large group of individuals who performed the Stroop test just once While these data are interpreted to suggest that preoperative cognitive impairment is a risk factor for postoperative cognitive impairment, we believe that they reflect that a small proportion of patients were bad at performing the Stroop test on their first assessment because of their increased age or lower premorbid IQ. However, in some of these patients, performance on the Stroop test improved with practice so that they were no longer classified as impaired. Indeed, eight (62%) of the premorbid 'impaired' patients were unimpaired by 6 months. It is unlikely that these patients were brain damaged at the preoperative assessment as suggested. We believe that the suggestion that cardiac surgery ameliorates cognitive dysfunction, is fanciful. Furthermore, a decline for an individual within the impaired category may be indicative of a much smaller change and thus have less impact, than a decline from a classification of unimpaired to impaired within an individual.

Previous studies have used group mean comparisons pre- and postoperatively and individual change scores,[3] while the present study design compares individuals repeatedly against the same normative group mean. These concerns would be negated if the classification of cognitive impairment were based on a metric that reflected the magnitude of change in cognitive performance over time, as each individual acts as their own control.[3] In fact, the reduced power arising from the use of a categorical definition of impairment could explain why the rate of post-surgical cognitive impairment (approximately 7%) was much lower than is generally reported (20–50%, see Symes and colleagues[4] for a review).

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1 Millar K, Ashbury AJ, Murray GD. Pre-existing cognitive impairment as a factor influencing outcome after cardiac surgery. *Br J Anaesth* 2001; **86:** 63–7
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4 Symes E, Maruff P, Ajani A, Currie J. Issues associated with the identification of cognitive change following coronary artery bypass grafting. *Aust NZ J Psychiat* 2000; **34:** 770–84

Editor—We are grateful for the interest of Maruff and colleagues in our study. First, on the matter of the Stroop test, they describe as 'incorrect' out statement that normative data for the test provide an indicator of 'likely' brain damage. We would refer readers to the Stroop manual,[1] where there is a description of the brain-damaged groups that contribute to the normative data, and the derivation of cut-off scores to 'discriminate normal and brain-damaged subjects'. The main appendix to the manual contains percentile equivalents of raw scores and 'indicates the likelihood of a given score being obtained by a brain-damaged subject'. The words 'likely' and 'likelihood' mean 'probable' and 'probability' respectively: they do not mean 'definite', and few would suggest that brain damage might be determined solely by a neuropsychological test. In our article, we observed that MRI studies have shown CNS abnormalities to exist *prior* to cardiac surgery, these being consequences of the long-standing disease state. Other authors have discussed the consequences of such *pre-existing* abnormalities in terms of diminished 'cognitive reserve' that may render patients more vulnerable to post-surgical cognitive deficits.[2]

Maruff and colleagues observe further that Stroop performance is related to both age and intelligence, as is the case with most tests of cognitive function. They suggest that patients who performed poorly were older and had lower pre-morbid IQ. The Stroop norms, however, take account of age so that the performance of older individuals can be evaluated against that of their peers, hence indicating the 'likelihood' that an individual's score reflects unusual impairment. Thus, while performance does indeed become poorer with age, it is the extent to which the individual's performance diverges from his or her age norm that is the issue.

Our suggestion that cardiac surgery might improve cerebral perfusion and hence facilitate cognitive performance is described by Maruff and colleagues as 'fanciful'. A more appropriate term would be 'hypothetical' because the proposal is amenable to an empirical test. We would add that others have been 'fanciful' before us. In addition to the 'perfusion hypothesis',[3] Heyer and colleagues[4] have hypothesized that cognitive improvement after cardiac surgery may indicate reversible impairment in neuronal function, or compensation by the brain through mechanisms that produce recovery after stroke. The difficulty is that many psychological medical and environmental factors may affect the patient's cognitive state after cardiac surgery, so that any explanation for improved performance must be speculative in the absence of a multifactorial prospective investigation.

Maruff and colleagues suggest that our finding of 7% impairment at 6 months is 'much lower than is generally reported'. They refer the reader to their own review which includes a tabular summary of 27 studies of short- and long-term

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outcome after cardiac surgery.[5] Eleven of the studies either made only short-term assessment or assessed function no later than 6 weeks after surgery. Fifteen of the studies are broadly comparable to ours in that long-term outcome was assessed at least 2 months or more after surgery. Whilst the summarized outcomes are necessarily scant in detail, it appears that seven of those studies found either that impairment had resolved at long-term assessment, or showed similar rates of impairment to our own. Thus, our result would seem consistent with almost half of the comparable studies cited of Maruff and colleagues.

Impairment rate is also dependent on the specific cognitive function being assessed, as cardiac surgery does not cause a global impairment of performance. For example, McKhann and colleagues[6] have shown very different rates of long-term impairment as a function of the assessment task (33% for complex figure copying, to 4% for psychomotor speed). In the case of the Stroop task, they found postoperative impairment to be 6% at 1 month, and 11% at 1 year. The figures encompass our rate of 7% with the Stroop test.

We acknowledge that our use of a binary outcome measure does, indeed, reduce statistical power, but given the available sample size we believe that this is a price worth paying to enhance the clinical relevance of our results. This is analogous to the distinction between a highly sensitive but rarefied 'explanatory' Phase II trial, which allows one to study underlying mechanisms, as opposed to a less sensitive but clinically-relevant 'pragmatic' Phase III trial.

As a final point, we would reiterate that our results are consistent with the 'Consensus Statements'[7,8] concerning methodologies for cardiac surgery research, in other words, that 'A number of patients presenting [for cardiac surgery] may have pre-existing CNS abnormalities [and where] the neuropsychologic state needs to be assessed [. . .] prior to operation to provide accurate baseline information'.[7] Our results suggest that pre-existing deficits may have implications for subsequent outcome, but they require independent replication and there would be merit as Maruff and colleagues suggest, in employing continuous rather than categorical measures of performance.

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1 Trenerry MR, Crosson B, DeBoe J, Leber WR. *Stroop Neuropsychological Screening Test Manual.* Odessa, Florida: Psychological Assessment Resources, 1989

2 Schmidt R, Fazekas F, Offenbacher H, *et al.* Brain magnetic resonance imaging in coronary artery bypass grafts: a pre- and post-operative assessment. *Neurology* 1993; **43**: 775–8

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5 Symes E, Maruff P, Ajani A, *et al.* Issues associated with the identification of cognitive change following coronary artery bypass grafting. *Aust NZ J Psychiat* 2000; **34**. 770–84

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Geodesic planes to facilitate the extension of alveolar liquid/air interfaces

Editor—Dorrington and Young[1] are right to remind lung physiologists that Clements and Tierney[2] stipulated that the liquid lining an individual alveolus can have no common surface connection with other alveoli, if lung stability is to be achieved, Only thus could different alveoli remain open by adjusting their surface tensions (γ mN m^{-1}) to different pressures (ΔP cm H_2O) across their liquid interfaces. The problem confronting Pattle,[3] and Clements and colleagues[4] some 50 years ago concerned the mechanism that prevented very small liquid-lined cavities from filling up if, and when, the available pressure, at functional residual capacity (FRC), might be less than 20 cm H_2O. (Unlike bubbles, the alveoli are open to the atmosphere.) Substituting values for pressure and histological radius of curvature in an alveolus at FRC, the Laplace equation suggested to Clements that the surface tension of the liquid had to be less than 10 dyne cm^{-1}, an inconceivable value for a water/vapour interface. (The surface tension of a water/vapour interface only approaches zero at the critical point, i.e. 374°C and 218.3 atm.) Nevertheless, over the past 50 years, innumerable papers have been published claiming that lung surfactants alone, could reduce the surface tension of such an interface to less than 10 dyne cm^{-1}. Cochrane and Revak[5] actually claim to have reduced the tension to zero!

Dorrington and Young quote our paper[6] as being the first to have drawn attention to the fact that films of lung surfactants, compressed beyond their equilibrium spreading pressure, become solid. It was this observation that provoked us to challenge the concept of surface tensions of less than 23 dyne cm^{-1}.[7–10] Initially, we suggested that it was the solid elements of lung surfactants, principally dipalmitoylphosphatidylcholine (DPPC), which is solid at 37°C, that might form an incompressible shell or barrier.[10] But an explanation was still required to account for the ease with which a lung, at FRC, can reflate given the relatively low air pressure (20 cm H_2O) and a liquid whose surface tension could not be less than 25 dyne cm^{-1}. The Laplace variables for curved surfaces are surface tension (γ mN m^{-1}), vapour pressure (ΔP cm H_2O) and radius of curvature (r). Clements accepted values for air pressure (20 cm H_2O) and assumed an alveolar radius of curvature (50 microns), predicting an operational surface tension of less than 10 dyne cm^{-1}. Using inappropriate devices for measuring surface tension, he and many others, ourselves included,[10] confirmed that almost zero pull could be obtained on a Wilhelmy dipping plate (the device commonly used to measure interfacial tensions).

But suppose the radius of curvature of the extending air/vapour interface was not that of the histological alveolus but negligible, even flat or planar as it might be between separating plaques or rafts of crystalline DPPC as described by a number of observers.[11–13] If a geodesic line is the shortest distance between two points on a curved surface, then the surface developing between separating plaques, themselves lying on a curved surface, would be planar, assuming of course, a zero contact angle between the headgroups of the DPPC and the water (Figure 1). For such a progression of events, the pressure required to deform a water/vapour interface having an infinite radius of curvature would, from Laplace, be minimal.

Perhaps the most appealing aspect of this idea is that it is now the radius of curvature of the extending surface of an alveolus that spontaneously adapts to the prevailing liquid surface tension (now any value between 20 and 70 mN m^{-1}) and air pressure <20 cm H_2O. This suggestion[9] no longer transgresses the conservative

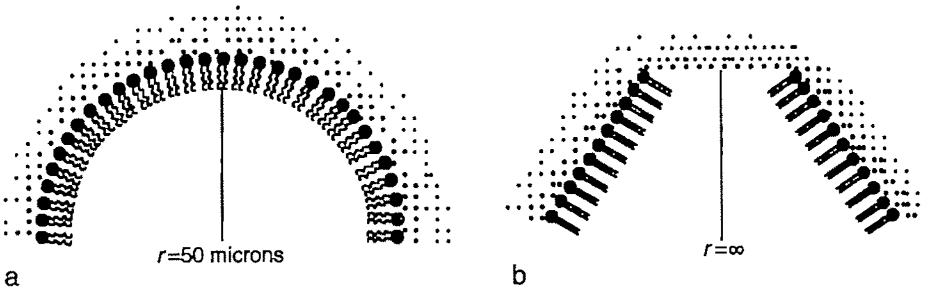

Fig. 1 (a) Illustrates a phospholipid lined alveolus with a radius of curvature of 50 microns. Equilibrium surface tension could be as low as 23 mN m^{-1} (b) Two plaques of solid phospholipid separating and initiating a geodesic plane of water, where surface tension could be as high as 72 mN m^{-1}.

values of liquid–vapour surfaces where a concentration difference of greater than a thousand-fold exists.

Wilhelmy dipping plates and pulsating bubble surfactometers remain excellent devices for offering operational assessment of lung surfactant activity but do not themselves measure surface tension or surface free energy as widely assumed by physicists.

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1 Dorrington KL, Young JD. Development of the concept of a liquid pulmonary alveolar lining layer. *Br J Anaesth* 2001; **86**: 614–16
2 Clements JA, Tierney DF. Alveolar instability associated with altered surface tension. In: *Handbook of Physiology, Respiration* 1964; **2**: 1565–83
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13 Nag K, Keough MW. Epifluorescence microscopic studies of monolayers containing mixtures of dioleoyl- and dipalmitoylphosphatidycholines. *Biophys J* 1993; **65**: 1019–26

Editor—Dr Bangham writes as a physicist to remind us that the surface tensions that are commonly entertained for a liquid–gas interface in the lung, namely values below 10 mN m^{-1} (dyne cm^{-1}), are 'inconceivable', though a reference to experimental work to substantiate this assertion would be helpful. He further reminds us of something that seems to have led to an immense amount of confusion in the literature: that, if a film of surface material lying at a liquid–gas interface becomes solid as the area of the surface is reduced, then standard techniques for measuring surface tension no longer measure true surface tension, or surface energy. They measure the structural properties of the whole solid film. Thus, the apparent reduction of surface tension to zero in some experiments probably arises because devices detect a resistance to compressions of a solid surface film, something referred to by analogy as 'reminiscent of Arctic pack ice' in the editorial to which Dr Bangham refers. An appreciation of these two points raised by Dr Bangham is important to understanding much of the literature on lung alveolar mechanics.

In the second half of his letter, Dr Bangham hypothesizes that the surface of alveolar liquid might consist of a succession of planar liquid and solid regions, forming a 'geodesic' structure. This is a fascinating idea that has little evidence to support it. Dr Bangham applies Laplace's equation (p=2T/r) to the planar liquid–gas surface in the centre of Figure 1b, and notes that, since the radius of curvature (r) is infinite, then the pressure (p) across the surface will be zero whatever finite value is taken by the surface tension (T). However, the geodesic structure illustrated in Figure 1b of Dr Bangham's letter is one that can sustain no surface tension in the planar liquid–gas surface, or tensile stress within the planar solid surface films that lie to either side of it. This can be seen by resolving forces at the junctions between the liquid and solid planar elements, where any tensile force along the surfaces of the planar elements would have a component that is unbalanced in a direction at right angles to the neighbouring planar element. Thus, the hypothesized structure appears to be incapable of sustaining *any* loading, and is unlikely therefore to be a suitable model for the alveolus.

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Sub-Tenon's anaesthesia—the local anaesthetic technique of choice for eye surgery?

Editor—I would like to thank Thind and Rubin[1] for their excellent editorial regarding local anaesthesia for eye surgery. Orbital anatomy is highly intricate and variable with numerous fine neurovascular structures coursing through the relatively restricted orbital space. Risks associated with periocular anaesthesia include damage to ocular nerves, direct puncture of blood vessels resulting in retrobulbar haemorrhage, and globe perforation.

Anaesthetists are concerned about placing a needle blindly into the crowded orbital volume and directing it back towards the orbital apex where the optic nerve and ophthalmic artery lie. In the current environment, there is greater emphasis on high volume cataract surgery increasingly necessitating the administration of the local anaesthetic by the anaesthetist, thereby dramatically increasing patient turnover. The surgeon and anaesthetist work synergistically, with the operator depending on the quality of block given in the anaesthetic room. A poor block can lead to a significantly increased risk of operative complication and consequent visual morbidity. Choice of anaesthetic varies from institution to institution and is, at present, highly dependent on personal preference.

Retrobulbar anaesthesia is losing popularity as it involves placement of a sharp needle intraconally in close approximation to the optic nerve and ophthalmic artery. Although the risks associated with the peribulbar technique are low, they are not insignificant. Globe perforation has significant sequelae related to marked visual morbidity, even if the injury is recognized and appropriate repair undertaken. Duker and colleagues[2] reported 20 cases of globe injury during needle-delivered ocular anaesthesia with only five eyes (25%) attaining a final visual acuity of 6/18 or better. Edge and Navon[3] retrospectively reviewed 50 000 retrobulbar and peribulbar blocks finding a 0.13% inadvertent scleral puncture rate, mainly associated with the presence of a posterior staphyloma. Approximately 40% of the patients who sustained a perforation in their series had a final visual acuity of 6/60 or worse. Arnold[4] prospectively studied more than 2500 consecutive peribulbar blocks, finding a 0.6% incidence of sight-threatening complications. Davis and Mandel,[5] in a large series of peribulbar anaesthetics, reported a 0.75% incidence of haemorrhagic complications.

These complications are unfortunately inevitable when needles are placed into the orbital cavity without an implicit understanding of orbital anatomy. Even in experienced hands variations in orbital anatomy, in particular the presence of a posterior staphyloma, may lead to inadvertent needle-related injury.

The editorial mentions the sub-Tenon's technique as an alternative when risk factors are present. I would suggest that the sub-Tenon's technique should be the method of choice in all cases where a regional anaesthetic is deemed necessary. The sub-Tenon's space is a potential plane that surrounds the globe. It is relatively avascular and is easily accessed via a small conjunctival incision. A blunt cannula is introduced and the local anaesthetic agent is injected slowly into the posterior sub-Tenon's space. This achieves excellent analgesia and akinesis with no risk of needle-associated neurovascular section or scleral puncture. The induced conjunctival chemosis rapidly resolves with no long-term sequelae.

Ripart and colleagues[6] compared peribulbar and sub-Tenon's block, finding that the latter gives significantly better akinesia, with improved rapidity of onset and more consistent effectiveness. Several other studies have directly compared peribulbar and sub-Tenon's anaesthesia, finding both methods to be equally efficacious.[7–9] To date, there have been no reported cases of complications associated with sub-Tenon's anaesthesia and, indeed, it has been the only method of local anaesthesia used in our unit for many years with no adverse events.

Although the risks of needle techniques are small, should a complication arise the visual consequences may be significant or even catastrophic. Do we not owe our patients a duty to choose an anaesthetic technique with proven efficacy, safety and a methodology that inherently reduces the chance of complication?

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1 Thind GS, Rubin AP. Local anaesthesia for eye surgery—no room for complacency. *Br J Anaesth* 2001; **86**: 473–6

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9 Kollarits CR, Jaweed S, Kollarits FJ. Comparison of pain, motility, and preoperative sedation in cataract phacoemulsification patients receiving peribulbar or sub-Tenon's anesthesia. *Ophthal Surg Lasers* 1998; **29**: 462–5

Editor—Thank you for the opportunity to comment on Alwitry's letter. We welcome and agree with most of what he says. We would, however, like to stress one or two points that we were trying to make in the editorial which Mr Alwitry has extrapolated, drawing conclusions which would in our view be premature

Most of the reported complications with sharp needle blocks occur when additional risk factors are present.[1] In experienced hands and with no particular risk factors, complications with peribulbar and shallow retrobulbar blocks are very uncommon.[2] Many experienced clinicians claim excellent results with well-established techniques and wish to continue their practice. It would be unfair to criticize that. Experience with these blocks spans several decades while the results of sub-Tenon's block are less well documented.

Many studies[3–5] have attempted to compare the efficacy of sub-Tenon's block with the more established technique. The evidence at this point is by no means conclusive. It is true that over this short period sub-Tenon's block has an excellent track record without reports of serious complications. There are signs that sub-Tenon's technique is gaining favour particularly with younger surgeons and anaesthetists. Maybe in the future, sub-Tenon's technique will prove to be the safest local anaesthetic technique for eye surgery. However, we feel that it would be premature to declare that it is the only safe way to provide local anaesthesia for eye surgery. Even so, it should be the method of choice when risk factors are present and akinesia is required.

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1 Duker JS, Belmont JB, Benson WE, *et al.* Inadvertant globe perforation during retrobulbar and peribulbar anaesthesia. *Ophthalmology* 1991; **98**: 519–26

2 Davis DB, Mandel MR. Efficacy and complication rate of 16,224 consecutive peribulbar blocks. A prospective multicenter study. *J Cataract Refract Surg* 1994; **20**: 327–37

3 Azmon B, Alster Y, Lazar M, Geyer O. Effectiveness of sub-Tenon's versus peribulbar anaesthesia in extracapsular cataract surgery *J Cataract Refract Surg* 1999; **25**: 1646–50

4 Briggs MC, Beck SA, Esakowitz L. Sub-Tenon's versus peribulbar anaesthesia for cataract surgery. *Eye* 1997; **11**: 639–43

5 Kollarits CR, Jaweed S, Kollartis FJ Comparison of pain, motility, and preoperative sedation in cataract phacoemulsification patients receiving peribulbar or sub-Tenon's anaesthesia. *Ophthal Surg Lasers* 1998; **29**: 462–5

Incidence of UK reactions involving rocuronium may simply reflect market use

Editor—Current concern over the propensity of rocuronium to initiate a hypersensitivity response appears overdone. The article recently published in this journal by Rose and Fisher[1] mirrors the UK experience as reported to the Northern General Hospital, Sheffield. The University Department of Immunology pioneered the centralized investigation of UK adverse anaesthetic reactions more than 25 years ago, and Sheffield still analyses in detail 100–200 anaphylactoid reactions each year. Its investigation protocols are broadly similar to those of Fisher and indeed to those of Laxenaire[2] in France. All three centres monitor reports reflecting similar reaction severity, the majority falling into Grades III and IV of the Ring and Messmer severity scheme[3] (i.e. those considered life-threatening).

The data tabulated here (Table 1) is for severe reactions implicating either an aminosteroid or a benzylisoquinoline neuromuscular-blocking agent (NMBA) reported for the years 1996–9. It simply compares the number of reactions in which a specific NMBA was administered against that which might be expected from its market use. I am indebted to Organon, Netherlands, for the 'normalized' market data used in the calculation.

There is clearly good correlation between the actual and the calculated figures for all four drugs and certainly no evidence to suggest excessive response to rocuronium.

As Rose and Fisher point out, the incidence of anaphylactoid response within any 'family' of drugs should be related fundamentally to the market use of that drug. However, it is not necessary that the sole mechanism should be that of IgE-mediated anaphylaxis as long as the mechanisms, including error, are random to each drug member. Marked discrepancy between actual numbers found, against those calculated, quickly reveals any outperformance indicative of some specific mechanism bias. In practice, such drugs (e.g. althesin) are rapidly excluded from the market unless they possess very advantageous clinical properties (notably succinylcholine). While not tabulated here, it can be stated that reactions involving succinylcholine each year exceeded the combined number of aminosteroid and benzylisoquinoline reactions, accounting for almost half of the total (all drugs) reports received, and revealing the extreme immunogenicity of this drug.[4]

In conclusion, the Sheffield findings are in agreement with the Rose and Fisher view that rocuronium has acceptable adverse reaction propensity akin to that of vecuronium and atracurium. However, contrary to the Australian view, over the study period 1996–9 there was no evidence whatsoever of a fall in either the overall number or the severity of anaphylactoid reactions reported. The much higher incidence of rocuronium reactions reported in France[2] is currently inexplicable and is likely to remain so if investigations continue to seek a purely antibody-mediated response as an explanation of all anaphylactoid reaction presentations.

Table 1 Distribution of benzylisoquinolines and aminosteroid NMBAs in UK reactions found and (predicted)

Year	*n*	Atracurium	Mivacurium	Vecuronium	Rocuronium
1996	46	21(21)	6(5)	19(12)	0(8)
1997	38	16(17)	2(4)	16(10)	4(6)
1998	56	22(26)	7(5)	17(15)	10(10)
1999	56	24(26)	7(5)	15(15)	10(10)
Total expected (*n*=196)		(90)	(20)	(51)	(33)
Total found (*n*=196)		83	22	67	24

Multiple drug use and unforseen drug–drug interaction (*in vitro* and *in vivo*) remain potent factors, not least from synergistic histamine release. Differences in site of administration (vein size) and speed of administration (bolus *vs* infusion) may represent geographical variations in clinical practice. While such factors will not increase the incidence of genuine IgE-mediated anaphylaxis, they may certainly increase the frequency of non-immune anaphylactoid mechanisms of identical clinical severity.

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1 Rose M, Fisher M. Rocuronium: high risk for anaphylaxis. *Br J Anaesth* 2001; **86**: 678–82

2 Laxenaire MC. Epidemiologie des reactions anaphylactoides peranesthesiques. Quatrieme enquete multicentrique. *Ann Fr Anesth Reanim* 1999; **18**: 796–809

3 Ring J, Messmer K. Incidence and severity of anaphylactoid reaction to colloid volume substitutes *Lancet* 1977; **I**: 466–9

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Are fade and sustained post-tetanic facilitation characteristics of typical succinylcholine-induced block?

Editor—It has been consistently stated in the literature that when succinylcholine is administered to patients with normal butyrylcholinesterase activity, a typical depolarizing neuromuscular block (phase I) develops. This block is characterized by the absence of fade to train-of-four (TOF)[1] or tetanic stimulation, and absence of post-tetanic facilitation.[2] Similar observations were noted in *in vitro* rat phrenic nerve diaphragm preparations.[3] TOF fade after succinylcholine is noted if volatile anaesthetics are used[1, 4] or if succinylcholine block changes from phase I (depolarizing) to phase II (nondepolarizing).[5]

I have noted, however, that following administration of a single dose of succinylcholine during propofol-narcotic-nitrous oxide-oxygen anaesthesia, recovery is characterized by the presence of both fade to TOF stimulation and sustained post-tetanic facilitation (Figure 1). Katz observed that after the first dose of succinylcholine, marked fade was noted on 50 Hz tetanic stimulation when the mechanical block was greater than 50%.[6] He also reported that the fade was not apparent when 20 Hz tetanic stimulation was used. On the other hand, although the upper panels of Figures 3 and 4 in his article clearly demonstrated sustained post-tetanic facilitation, Katz stated that 'Post-tetanic potentiation was *not* seen in the mechanical or electrical records during recovery from the first dose of suxamethonium'. Katz used nitrous oxide-opioid anaesthesia in his study. In patients reported here, anaesthesia was induced with midazolam 1–2 mg, propofol 2–2.5 mg kg^{-1}, fentanyl 250 µg and 70% nitrous oxide in oxygen, and was maintained with continuous infusion of propofol 50–150 µg kg^{-1} min^{-1} and 70% nitrous oxide in oxygen. Clinical studies have demonstrated no interaction between propofol and succinylcholine or nondepolarizing neuromuscular blockers.[7, 8]

There is evidence to suggest that succinylcholine reduces the presynaptic release of acetylcholine.[9] This prejunctional effect

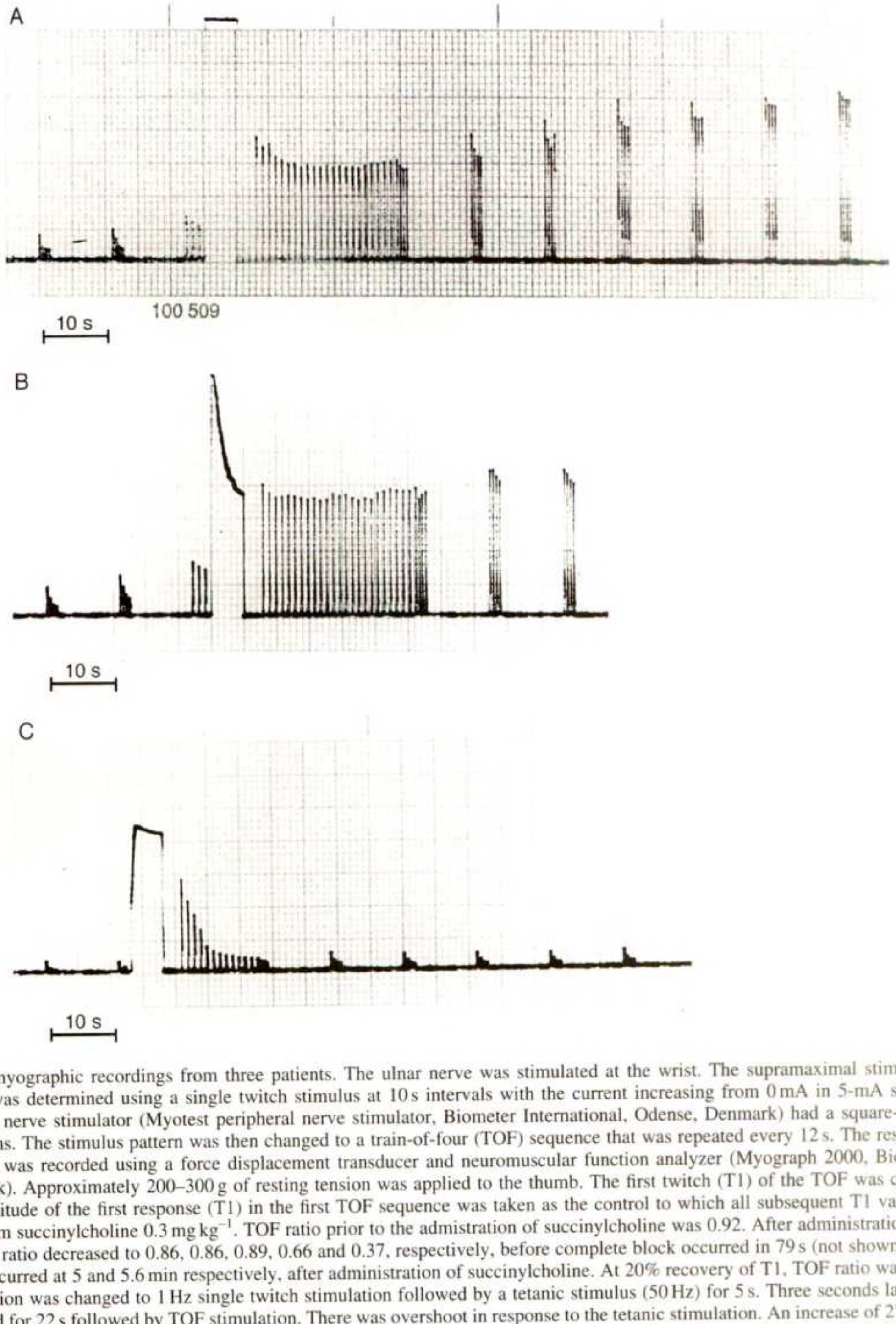

Fig. 1 Mechanomyographic recordings from three patients. The ulnar nerve was stimulated at the wrist. The supramaximal stimulus at the adductor pollicis muscle was determined using a single twitch stimulus at 10 s intervals with the current increasing from 0 mA in 5-mA steps.[10] The stimulus generated by the nerve stimulator (Myotest peripheral nerve stimulator, Biometer International, Odense, Denmark) had a square-wave formation and duration of 200 ms. The stimulus pattern was then changed to a train-of-four (TOF) sequence that was repeated every 12 s. The resultant contraction of adductor pollicis was recorded using a force displacement transducer and neuromuscular function analyzer (Myograph 2000, Biometer International, Odense, Denmark). Approximately 200–300 g of resting tension was applied to the thumb. The first twitch (T1) of the TOF was considered the twitch height. The amplitude of the first response (T1) in the first TOF sequence was taken as the control to which all subsequent T1 values were compared.
(A) Recovery from succinylcholine 0.3 mg kg^{-1}. TOF ratio prior to the admistration of succinylcholine was 0.92. After administration of succinylcholine 0.3 mg kg^{-1} TOF ratio decreased to 0.86, 0.86, 0.89, 0.66 and 0.37, respectively, before complete block occurred in 79 s (not shown). Recovery of T1 to 10% and 20% occurred at 5 and 5.6 min respectively, after administration of succinylcholine. At 20% recovery of T1, TOF ratio was 0.4. Thereafter, the mode of stimulation was changed to 1 Hz single twitch stimulation followed by a tetanic stimulus (50 Hz) for 5 s. Three seconds later, the single twitch was again applied for 22 s followed by TOF stimulation. There was overshoot in response to the tetanic stimulation. An increase of 270% was noted in the immediate post-tetanic twitch height compared to the pretetanic value. Three seconds later, a plateau of post-tetanic twitch height was noted (215% compared to the pretetanic value). Thereafter, TOF ratio recovery preceded at a higher value from that noted before tetanic stimulation.
(B) Recovery from succinylcholine 0.5 mg kg^{-1}. TOF ratio prior to admistration of succinylcholine was 0.96. After administration of succinylcholine 0.5 mg kg^{-1} TOF ratio decreased to 0.94, 0.92, 0.88, 0.35, 0.57 and 0.27, respectively, before maximum block occurred in 90 s (not shown). At 20% recovery T1, TOF ratio was 0.4. Fade in response to tetanic stimulation is noted. An increase of 285% was noted in the immediate post-tetanic twitch height compared to the pretetanic value. Note the sustained plateau of post-tetanic twitch height. As noted in the upper panel (A), TOF ratio recovery proceeded at a higher value from that noted before tetanic stimulation.
(C) Recovery from mivacurium 0.1 mg kg^{-1}. Tetanic fade and *unsustained* post-tetanic facilitation are noted during recovery from a nondepolarizing block. An increase of 700% was noted in the immediate post-tetanic twitch height compared to the pretetanic value.

could explain the fade phenomenon.[9] It is difficult, however, to explain the sustained responses observed after tetanic stimulation. The characterization of succinylcholine-induced neuromuscular block should be re-examined and further studies are needed to better understand the uncertainties in neuromuscular pharmacology that still exist.

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Trans-Atlantic variation in response to neuromuscular blocking drugs

Editor—In 1969, we reported London patients to show a diminished responsiveness to succinylcholine and tubocurarine as compared with their counterparts in New York.[1] Later, Fiset and colleagues[2] found a similar disparity in the response to vecuronium in patients in Paris and Montreal.

One of us (JN) has been reading the papers of the Medical Research Council's Anaesthetic Committee that met between 1923 and 1948. When neuromuscular block was becoming an accepted tool, there was some discussion as to the relative merits of Intocostrin and d-tubocurarine. In April 1947, Dr H.S. Newcombe from Squibbs—the US firm making both Intocostrin and tubocurarine—wrote to the MRC. The letter ends: 'We have noticed both in private communications and in British publications, discrepancies in the clinical dosages of our preparations and those of British origin, relatively more of the British preparation being used. We have assayed the British drug and believe it to be substantially identical to our own d-tubocurarine chloride. We therefore have to presume that the discrepancies are due to the wide latitude in dosage which may be found clinically useful or appropriate'.

It appears that we were not the first to note the differences in responses.

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1 Katz RL, Norman J, Seed RF, Conrad L. A comparison of the effects of suxamethonium and tubocurarine in patients in London and New York. *Br J Anaesth* 1969; **41**: 1041–7

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Book Reviews

Principles of Physiology for the Anaesthetist. 1st Edn. I. Power and P. Kam. Published by Arnold, London. Pp. 399; indexed; illustrated. Price £35. ISBN 00340742135

Here is a puzzle. For £24.99, I can buy the 851 pages of the 19th edition of a standard textbook of the whole of physiology. For £10 more, I can buy the 1064 pages of the 10th edition of another standard textbook. On the shelves of the bookshop where I found these two books (recent editions of which are both on my own bookshelves), were three other textbooks of medical physiology, all with double the amount of material but costing less than *Principles of Physiology for the Anaesthetist.* Two of the standard textbooks had good key point or summary boxes as well as self-assessment exercises for each chapter; all but one of the books had one or other of these useful features.

So the puzzle is why anyone should choose to buy a more expensive book (at least in terms of information per pound), which has neither key points nor self-assessment?

What is physiology for the anaesthetist anyway? How is it different from what other books tend to call medical, or general, physiology? The answer is that it is not different but that anaesthetists place more emphasis on the respiratory and circulatory systems than, say, gynaecologists, who need detailed information about female sex hormones. A whole set of textbooks probably have been or are being written entitled physiology for the gynaecologist, bacteriologist, orthopaedic surgeon, and so on. They are aimed, as this book is, at the examination candidate, but it seems more sensible to buy a general textbook and to supplement it if necessary with one of the smaller monographs on the aspects of physiology particularly relevant to the specialty.

There is nothing wrong with this first edition of Power and Lam that a bit more attention to detail will not solve. Some of the diagrams are carelessly drawn; for example, the pulse pressure wave on page 102, and the expired carbon dioxide trace on page 85 that suggests a slight decrease towards the end of expiration. The index is well laid-out, but my page-flicking revealed that it is missing afterload, dyspnoea and surfactant, and that epinephrine is in the wrong place. These typographical details are easily correctable, but the missing physiological detail is more worrying.

There is nothing wrong with this book in the sense that an examination candidate for the Primary FRCA will pass if they know the book's material well. But it is too superficial to be an 'invaluable reference throughout anaesthetic training and beyond', and it is not consise enough to be 'a useful revision aid'. It would be better to buy a standard textbook, a monograph on respiratory physiology, and a book of physiology lists (with the appropriate CCST handbook from the College) for revision

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Anaesthesia Databook. 3rd Edn. Rosemary Mason. Published by Greenwich Medical Media Ltd., London. Pp. 624; indexed. Price £50. ISBN 1841100676.

What do you do when you find a patient with an unusual condition on your operating list or, worse, you are telephoned at night for advice about a complex medical problem? The *Anaesthesia Databook* by Rosemary Mason is aimed at the experienced anaesthetist facing just such a problem. This clear, concise and consistent text would provide enough information to greatly assist emergency management, while each topic is supported by a list of useful and up-to-date references if time permits more extensive preparation. This material would also provide a good starting point when preparing a lecture or seminar. With the increasing importance placed on CME and maintaining 'core skills' at dealing with unusual emergencies, this book could have a whole new purpose. Although primarily aimed at the more experienced anaesthetist, the book would undoubtedly have a place in examination revision as well.

The third edition of this useful book demonstrates a further evolution in layout from earlier incarnations and is now divided into just two sections. The first section is by far the dominant, comprising 90% of the text; it covers medical disorders and anaesthetic problems. Over 200 conditions are listed, in alphabetical order, most of which are dealt with in a standardized format. This generally consists of a brief description of the condition, a list of preoperative abnormalities, a list of anaesthetic problems, a series of key points in perioperative management, and a brief bibliography. The style is consistent, reflecting the single author, and is generally concise, practical and to the point. There is little basic information; the book is not aimed at the novice, but the more experienced anaesthetist will find most of what they need to know in the acute situation. Where controversy exists, the strength (or weakness) of the evidence supporting the current recommendations is neatly summarized. Thus the author has combined the treacherous tasks of providing a balanced overview while still offering practical advice for the 'real-world' situation. No doubt some will disagree with a few specifics within the advice given, but overall the value of this section is enormous.

The second section covers anaesthetic problems arising during anaesthesia, as distinct from pre-existing conditions. Again, the format is fairly consistent, comprising a thorough description, the presentation, diagnosis and/or associated problems, management and a bibliography. This section is again extremely useful and contains current, practical advice on 26 conditions ranging from Addisonian crisis to TURP syndrome.

Although not a new book, the third edition has been thoroughly revised and updated to take account of advances in evidence-based medicine, better understanding of the pathophysiology of a variety of conditions as well as developments in anaesthetic drugs, techniques and monitoring. Management of the obstetric patient is included for many of the conditions described in this latest edition, which also contains some problems specific to obstetric anaesthesia. Compared to the earlier editions of the book, the sections on miscellaneous and rare and unusual syndromes have been removed. The esoteric may have gone, but any pathologies which are at all likely to be encountered by the average anaesthetist are contained within the main section. This is a better layout, as the reader no longer has to first consider whether the condition of interest is 'uncommon' or not. The alphabetical listing now makes the comprehensive index almost superfluous, although it is occasionally useful; for example, sickle cell disease is grouped under 'haemoglobinopathies' rather than having its own entry. A section from earlier editions on normal values has also been omitted; such data are readily available and in any case often vary between different laboratories. A single appendix contains a list of 'useful' addresses, telephone numbers and websites. Some of these are for general bodies, such as the Association of Anaesthetists and the Royal College of Anaesthetists, which are already widely available, although those of more specialist centres are genuinely useful. This section can

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hardly be criticized as superfluous, however, since it occupies only two out of more than 600 pages.

There is little to object to in this excellent reference book. The page numbers are quirkily placed half-way up the side of the page, but they blend in nicely with a clear index letter and box containing the main topic on that page. The feel is therefore rather like the equally useful *Yellow Pages* and finding the desired information is a similarly rapid process. There are no illustrations or diagrams, yet the style of short paragraphs and numbered 'bullet points' ensures that their omission does not make the text heavy going.

The usefulness of this book is such that there is little real competition. A few other books list coexisting diseases, but they rarely offer more than a line or two on perioperative management. The closest rival is probably *Anaesthesia for Uncommon Diseases*. While this may cover more pathology, most of the additional conditions are very uncommon indeed. Furthermore, the *Anaesthesia Databook* has a much more consistent style than that multiauthor text and in many cases provides far more practical information on anaesthetic management.

This book should be widely available in emergency theatres and within anaesthetic departments. Consultants covering the general on-call rota may be reassured by having their own copy at home. No doubt many copies of previous editions are in such use, but there is sufficient new or updated material in the present version that an update would seem worthwhile, especially as the price is now lower than 6 years ago! If, for some reason, you are not already familiar with this book, then I would definitely recommend that you should go out and buy a copy immediately.

I. Smith
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Practical Fibreoptic Intubation. M. Popat. Published by Butterworth-Heineman, Oxford. Pp. 191; indexed; illustrated. Price £30. ISBN 0750644966.

Performing fibreoptic intubation requires practical skills, and the only way to acquire these is through 'hands-on' experience in real patients. This book is not intended to be a substitute for clinical experience but aims to provide the practical information upon which fibreoptic skills can be based. Its goal is to prepare novices for training, to help competent endoscopists develop their skills further, and to give guidance on teaching techniques. This slim volume, written with the sure-footed air of someone who performs and teaches fibreoscopy on a day-to-day basis, succeeds admirably in achieving these aims.

The first half of the book deals with the principles underlying the practice of fibreoptic intubation. The first chapter gives a description of endoscopic equipment and later on there is a chapter detailing the airway aids used in conjunction with fibrescopes. The ideas behind the organization of training programmes are set out and there is a welcome, though brief, discussion about patient consent for fibreoptic training. Many anaesthetists are concerned about this ethical dilemma and a more substantial presentation of the relevant arguments would have been useful The clear and concise account of fibreoptic intubation in difficult airway management is excellent.

The two main themes of the second half of the book are 'how to do it' and 'how to teach it'. We are given detailed descriptions of fibreoptic intubation in anaesthetized patient with both the apnoeic and the spontaneously breathing techniques. I was not convinced about the need to conduct some training with patients in the unstable lateral position. The technique of face-to-face endoscopy, which is essential when managing patients in the sitting position, can be rehearsed safely and satisfactorily by simply standing at the side of the supine patient. I was also concerned that trainees were allowed a second attempt at endoscopy, after re-ventilation of the patient's lungs, if they failed the first time. I think this practice might be difficult to justify in the present climate, even if the patient has given expressed consent for it to be carried out. Particular prominence is given to awake intubation with chapters focusing on general considerations, local anaesthesia, and practical techniques. There is a helpful chapter on how to overcome difficulties during fibreoptic intubation, but the section on the inability to advance the fibrescope through the nose could have been more informative, particularly as it includes a photograph showing an obvious septal deviation. Other highlights include fibreoscopy in paediatrics, in the tube changing, and in double lumen endobronchial tube placement and position check.

The book is easy to read, comprehensive and well referenced. The subject is clearly presented and much sound advice is given. The author always tries to provide evidence-based arguments before making recommendations. The text is well organized with many bulleted lists and boxed tables. The photographs and illustrations are of a uniformly high standard. This book's target audience is potentially huge. Any anaesthetist, senior or junior, who wants to learn, to improve, or to teach fibreoptic intubation, should benefit from reading it.

J. E. Smith
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Critical Care Focus. H. F. Galley (editor). Number 5: *Antibiobic Resistance and Infection Control.* Published by BMJ Books, London. Pp. 54 Price £14.95. ISBN 072791538X.

This is a useful book on antibiotic resistance and infection control in the intensive care unit (ICU). Although written by 10 authors, it is too concise (54 pages). It is one of a series of five issues entitled *Critical Care Focus*, which has an editor and an editorial board of four members of the Intensive Care Society The book has seven chapters, which contain only seven figures, two tables and five summary boxes. The introduction is a summary of the chapters. But this issue does contain valuable information and is easy to read. The first chapter includes useful ideas and data. Nomination of an ICU infection lead, which we have in our ICU, is timely. Since many of the problems of infection and antibiotic resistance are imported to the ICU from the wards, the idea of an infection lead should be extended to the wards, which we are also attempting to introduce Involving microbiologists and pharmacists in the management of infection is another good idea.

The chapter on catheter-related infection is comprehensive, but the role of plastic devices in the resistance problem is not discussed.[1] The chapter on mechanisms of antibiotic resistance is also well written and clear. The book contains useful hints on patients' microbiology and optimizing the use of antibiotics. The value of basic hygiene and isolation for infection control is highlighted. Rotating antibiotic regimens to avoid emergence of resistance, and risks of prophylactic antimicrobials are also discussed. However, having read this update the reader would still have difficulty to design a policy to control antibiotic resistance.

Three main components contribute to endemicity of resistant potential pathogens. Each account for about a third of the problem. They are: (i) import of resistant micro-organisms; (ii) antibiotic usage exerting selective pressure and promoting gut overgrowth; and (iii) transmission of resistant micro-organisms *via* hands of carers. The issue of patients admitted as carriers of resistant micro-organisms to the ICU is not discussed. Although we support good hygiene practices, hand washing fails to prevent infection with resistant pathogens carried by patients in their 'admission flora'. Only surveillance samples of throat and rectum enable the intensivist to identify patients who 'import' resistant bacteria to the ICU. Early detection of import is integral to the control of endemicity of resistant micro-organisms, as immediate isolation and subsequent eradication of the abnormal carrier state is required to prevent spreading into the ICU. Hence, surveillance cultures have a role to play.[2] Chastre does not appear to be in favour of the use of routine surveillance cultures, although Bion states that clinical assessment needs to be supplemented by microbiological data. The authors agree that normal flora plays an important role in the control of abnormal potential pathogens that are often resistant to different antimicrobials. Two studies showing that amoxycillin disregards ecology and promotes overgrowth of resistant mutants in the large inoculum of the digestive tract are discussed. There is a correlation between antimicrobials that respect ecology and discourage antimicrobial resistance, whilst antibiotics that disregard ecology have been shown to promote overgrowth and expression of resistant mutants amongst the high concentration of faecal micro-organisms.[3] A table classifying antimicrobials into 'flora sparing' and 'flora friendly', in the last chapter of Gant, would have been useful.

Chastre discusses his own study that shows that invasive methods to diagnose pneumonia, whilst reducing antibiotic usage, save lives compared with non-invasive tracheal aspirates. However, the mechanism of survival is unclear and the incidence of resistance was identical in both groups. Humphreys discusses the means aimed at control of transmission of micro-organisms. He acknowledges that infection control guidelines are based on expert opinion rather than on results of randomized trials.[4] For example, hand washing has never been shown to reduce pneumonia in the ICU setting. Yet, all research into infection control practices has some endpoints that do not relate to patients, including compliance of hand washing amongst healthcare staff. Selective digestive decontamination (SDD) may play a role according to Bion. The literature[5] does not support Gould's statement that eradication of resistant pathogens using SDD has proved disappointing, and a recent publication suggests that the use of oral non-absorbable antibiotics may prolong the antibiotic era.[6] Despite more than 15 years of ongoing controversy, SDD has not gone away!

Antibiotic use will continue to depend upon the balance between the risk and benefit to the patient. This book, in our opinion, is good in parts but falls short in important areas.

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1 Steinberg JP, Clark CC, Hackman BO. Nosocomial and community acquired *Staphylococcus aureus* bacteremias from 1980 to 1993: impact of intravascular devices and methicillin resistance. *Clin Infect Dis* 1996; **23**: 255–9

2 Damjanovic V, van Saene HKF. Outbreaks of infection in neonatal intensive care units *J Hosp Infect* 1997; **35**: 237–44

3 Lacey RW, Lord VL, Housan GL, *et al*. Double blind study to compare the selection of antibiotic resistance by amoxycillin or cephradine in the commensal flora. *Lancet* 1983, **2**: 529–32

4 van Saene HKF, Silvestri L, de la Cal MA. Prevention of nosocomial pneumonia in the intensive care unit. *Curr Opin Crit Care* 2000; **6**: 323–9

5 Taylor ME, Oppenheim BA. Selective decontamination of the gastro-intestinal tract as an infection control measure. *J Hosp Infect* 1991; **71**: 271–7

6 Baines PB, Meyer J, de la Cal MA. Antimicrobial resistance in the intensive care unit: the use of oral non-absorbable antimicrobials may prolong the antibiotic era. *Curr Anaesth Critical Care* 2001; **12**: 41–7

Self Assessment Colour Review of General Critical Care. H. Mathilda Horst and Riyad Karmy-Jones. Published by Manson Publishing Ltd., London. Indexed; illustrated. Price £15.95. ISBN 1874545863.

A picture is worth a thousand words and, as a result, any colour review is a great help to practitioners of intensive care medicine. This small book presents interesting situations portrayed in pictures, followed by a summary, with questions and answers. The book is a reasonable size with good quality illustrations. Inevitably it concentrates on what can be photographed or easily illustrated, covering a wide breadth of topics of relevance to intensive care, with perhaps a surgical emphasis. The cases are presented in a random order, which makes this a 'dipping in' book, but as a form of revision it would have been better presented by body systems. Had a more systematic approach been taken, then a more balanced spread of cases might have resulted and there may have been the opportunity to illustrate key areas of evidence-based practice, which is not attempted.

The target audience is said to be senior medical students, critical care/intensive care specialists and surgeons in training. All these groups will find the book interesting. Perhaps the critical care specialists will find the approach the most unusual and may well benefit from the somewhat surgical stance taken through this North American text and the slightly different perspective it brings. This is particularly so with the questions posed around many of the case summaries. It is worth being clear that this book is not designed to help with examination or to aid revision in a systematic way.

In summary, this book is a worthwhile text that can be easily dipped into and it represents reasonable value for money.

Gary H. Mills
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CD Review. A-ware: Study Edition. Multilingual Simulation Software for Anaesthesiology. Published by Springer-Verlag, Heidelberg. Price £108.39. ISBN 3540148663.

I am a keen user of PC-based simulation software, and so was very interested in 'A-Ware· Study Edition'. My first impressions from the box were that I needed Visual Basic or Visual C++ to run the software, since they are emblazoned on the back in large blue letters. Not so, and I fail to understand why the end-user needs to know what languages the programmers worked in. The program installed easily on several PCs that I tried, and the quoted specifications of a 'Pentium PC' and Windows 95/98 or 2000 with 32 Mbytes of RAM and 800×600 resolution are unlikely to put off most potential purchasers. My only problem was customizing A-ware to work on my notebook PC; the widescreen ratio of my display (800 by 480) meant that I had to frequently scroll up and down to see both the surgeon's comments and the ECG. Widescreen is now a common feature on contemporary notebook PCs that the authors would be wise to consider. Enthusiasts will be pleased to know that, although this program usually requires the CD to be present when it is run, the 3rd party utility '*virtual CD*' means that this requirement can be omitted.

The program launches into a movie, which gets boring after the second use of the software and can be avoided by a single click of the mouse. One is then presented with the rather restrictive 19 separate scenarios, which can neither be edited nor added to in this, 'Study', version. The more expensive 'Professional' version promises more scenarios, but I did not get the opportunity to review it.

Once our virtual patient is selected, a science fiction-style combined anaesthetic machine, multi-parametric monitor and video screen appears as a single entity, totally hi-jacking windows (except for the screen saver) until the end of the session. Unused monitor options (e.g. from an arterial line, usually set up before the simulation begins), still appear as flat lines on the display. Dr McCoy from *Star Trek* will be familiar with the mouse-click data entry required to set the gas flows, inject hypnotic agents etc but contemporary anaesthetists will not. The user interface is appalling, and could so easily have actually required more life-like data entry (e.g. one to virtually 'turn' the vaporiser dial rather than tapping in a number).

The virtual surgeon will not start work until our virtual patient is anaesthetized and subject to competitive neuromuscular blockade; spontaneous respiration is not simulated unless the patient is awake. In fact, the insight of the virtual surgeon extends to stating that the patient is inadequately anaesthetized even during profound neuromuscular blockade, a measurement that many real-world anaesthetists find problematic.

Time travels at twice 'real time' in this simulator. Time can be speeded up during boring procedures. Since only 10 min are allowed for recovery after the cessation of surgery, and this amounted to 5 min on the simulator, I was left with the feeling that recovery was always rushed.

The physiological model (Guyton *et al.,* 1972) is well documented and seems to work in a realistic manner for some parameters. Others, such as the 'hypnometer', were a revelation to me. I want to buy one in real-life! It was not any of the currently available commerical monitors of anaesthetic depth (according to A-ware's help pages), and so, as a simulated variable, the hypnometer is at best potentially misleading. A quirk that I observed during one rather problematic scenario was that the digital display of the hypnometer did not correspond with the level of hypnosis presented on the bar graph display

The multi-lingual nature of the software is implemented in an imbalanced way. Spellings are US English in software and UK English on the box. More importantly, US and international drug usage/dosage is given in help files (which are in Word-compatible files), but not the UK guidance from the BNF

Another regional quirk was the inability to simulate simple disconnection from the anaesthetic circuit for transfer of the patient to the operating room from a separate anaesthetic room. This could only be achieved by successive virtual extubation and re-intubation, which initiated unwanted effects from the physiological model.

My biggest impression of this software is one of missed opportunity. Sound is poor, simply emulating the pulse, and much would have been gained from real surgeons comments, rather than subtitles, and realistic operating room noises (such as airway sounds). Visually, it should have been possible to present different 'skins' to realistically emulate the monitors currently available, so that one could customize the simulator to look like one's own equipment, or, more interestingly, to evaluate monitors that one might like to use. These could be made available on the Internet for download. The software does not permit this. Also, the ability to input one's own data from anaesthetic records would have been useful, allowing 'what if' exercises to be conducted as an aid to teaching and CME.

I was left wondering who are the target purchasers? Non-anaesthetists (especially hospital administrators and medical students) will benefit from using this program to gain an outline understanding of the speciality (it invoked just the right level of fear in a naive user). Trainees will readily bore of the 19 pre-defined simulations, and so I suggest they buy the more expensive 'Professional' edition More senior users will perhaps use the program to brush up on their knowledge of newer agents that are not part of their routine practice. Any prospective purchaser would be well advised to try this software before they buy.

If coupled with a virtual professional mentor, a virtual courtroom and more dramatic scenarios, this simulation could be a best-selling computer game!

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CD Review: Central Line and Arterial Line Insertion. Published by Dumas Ltd, London. Price £25. Computer requirements: PC, Windows 95 or higher, Pentium 133 Mhz processor, soundcard, 80×600 16-bit display, speakers.

Just as the dot.com revolution was decidedly unimpressive, so the promise of CD-ROM education has been sadly disappointing to date. This CD-ROM sets out to explain how to insert a central venous line, a peripheral arterial line and a peripheral venous line. Is it better than one of the many chapters already published on paper? It is certainly less convenient to use. It cannot be read in an odd moment between cases or kept on the nurses' station in the ICU for that very occasional idle moment. Using a CD-ROM requires a certain amount of commitment and, if this medium is going to succeed, then it has to offer much more than a computerized book narrated by an actor for those people who cannot be bothered to read for themselves. There is much that is good in this CD-ROM but it could be so much better. Practical procedures are best learned by watching them being performed. This CD offers only a series of still photographs within a relatively small frame. Where are the video clips? The narrative is clear but why is the last sentence of every section truncated so that the last one or two words are lost?

On opening the CD-ROM one is presented with an advertisement for the locum agency that sponsored its production. This unexpected, compulsory brush with commercialism tends to evoke a similarly hard-nosed response in the user. If this CD was sponsored, why am I expected to pay £25.00 plus carriage for it? The advertisement fades to reveal the central worksurface, laid out pleasantly with a text frame on the left, a photo frame on the right and a row of icon buttons across the top of the screen. One of these icons depicts a red telephone and is labelled 'contact'. Is this the route to an internet-based helpline? No. Click on the telephone icon and yet moe advertisements appear—this time in the form of the website addresses for the publisher and, you guessed it, the locum agency.

The other icons open chapters on arterial, central venous and peripheral venous line insertion and a chapter entitled 'Wash and Glove' (no adverts this time). Having chosen a chapter it can be viewed in sequence by simply clicking on the 'next' button after each short text paragraph on the left of the screen, which is accompanied by a photograph or diagram on the right of the screen. An alternative is to use a second row of icons to jump directly to a particular paragraph; for example 'contraindications' or 'anatomy'. There is a 'top tips' icon that flashes at particular points in the chapter. This is a nice touch.

There is a very good 'patient/professional interaction' section. The doctor looks the part, shakes hands with the patient and introduces himself before explaining what he intends to do. Unfortunately, this section is not tailored particularly well to the individual chapters and, because it is largely generic, it is appropriate to some of the practical procedures but not to others. A section on 'patient monitoring' suffers from the same shortcoming but is otherwise very competent. There are one or two appallingly vague instructions. The viewer is exhorted to take the patient to 'an environment appropriate to the procedure' but there is no indication as to what the appropriate environment might be. Similarly, 'a brief general examination is essential' and 'check that necessary pre-operative interventions have been performed' are the only recommendations. The practitioner is reminded to 'review the results of any investigations'—but *which* investigations?

The antomical diagrams are very poor—not just my opinion but also that of every trainee to whom I showed them. In general, they are unclear and confusing. The diagram of the anatomy at the wrist seems to show the ulnar artery in an incorrect relation to the ulnar nerve. The photographic description of neck line insertion shows the right side of the neck—why does the accompanying anatomical diagram show the left side of the neck?

Peripheral cannulation is indifferently covered. I was pleased that a skin antiseptic is recommended and the disposal of 'sharps' is covered. There is no mention of how to choose the best vein on the back of the hand or how to decide what size of cannula to use. No mention is made of veins in the forearm. At the end of this section, I clicked on the 'help' icon and was faced with a blank screen that could not be restored by pressing the 'Esc' key and necessitated re-booting the computer. What a pleasure to see that locum agency advert again!

Arterial annulation is covered more comprehensively. There is a good list of indications but the list of relative contraindications includes the caveat to avoid an end-artery without further explanation. There is no mention of choice of arterial cannula or of the Seldinger technique.

Central venous line insertion is the section that is likely to be of the most interest to trainees. The approaches covered are the 'low approach', the 'high approach', the 'middle approach', the 'supraclavicular approach' and the 'infraclavicular subclavian approach'. The infraclavicular subclavian approach is not well covered and the surface markings for the needle entry site are not shown. There is a poor photograph of a tunnelled line. The list of relative contraindications could usefully include reference to the avoidance of a second attempt at cannulation on the contralateral side because of the risk of bilateral pneumothorax—yes, it has happened.

The patient/professional interaction information is rather vague—in particular in relation to the acceptable limits of coagulation tests. The respiratory review could easily be improved by relating clinical signs to the underlying pulmonary pathology. The list of complications should include haemothorax. I was puzzled by the reminder to 'check that the necessary pre-operative interventions have been performed'. ECG monitoring is wisely recommended but no mention is made of pulse oximetry. A useful tip, omitted in this CD-ROM, is to switch-on the tone function of the pulse oximeter to assist the practitioner in detecting Seldinger wire-induced arrhythmias without having to have an assistant to continuously scrutinze the ECG display.

The anatomy illustrations are poor and confusing. The hyoid bone is illustrated but not the cricoid cartilage, which is an important landmark for the middle approach. It would be useful to have arrows appear on the clinical photograph to better illustrate the anatomy. Once again, the authors need to be more specific. For example, they advise advancing the needle 'no more than a few centimeters'—is 'a few' 2 cm or 5 cm? The description of each procedure is generally well covered but, astonishingly, the patient's unsterile theatre cap is encroaching on the sterile field by at least 3 cm. In one photograph, the operator's gloved hand actually appears to be touching the theatre cap. There is no mention of the danger of shearing-off part of the Seldinger wire if it is withdrawn through the needle. There is no mention of the, arguably safer, 'through a cannula' rather than the 'through a needle' technique. The narrative fails to mention that many practitioners make a skin 'nick' with a scalpel before inserting the needle or, at least, before inserting the dilator. There is no recommendation that each lumen of the central line should be flushed *before* insertion to check their patency. Antibacterial spray is recommended before application of a transparent dressing. Am I alone in finding that these powdery sprays prevent adequate adhesion of the transparent dressing? 'Standard nursing observations' are recommended after line insertion—this recommendation is vague to the point of being totally unhelpful.

It was refreshing to see the chapter entitled 'Wash and Glove' In the halcyon days, theatre sisters had the time to teach medical students how to 'scrub' but, currently, this art is taught badly, if at all. The photographs are of good quality but the narrative is confusing in several places and the process of donning gloves would be made much clearer if video clips were used—their lack spoils this important chapter.

It is difficult to sum up this CD-ROM. A great deal of time and thought has clearly been spent on its production. The lack of video is a major disadvantage and there are many areas that need to be crisper. As it stands, it would be a useful addition to the ICU or anaesthetic department library. But my personal inclination would be to wait for the second edition that I hope will follow.

N. J. N. Harper
Manchester

British Journal of Anaesthesia **87** (3). 530 (2001)

Erratum

Book review: *Bonica's Management of Pain*, 3rd Edn. (*BJA* 2001; **86**: 905)

This book review referred to Dr Bonica as aged 83. The Editor-in-Chief has been informed that this is incorrect and unfortunately Dr Bonica died some years ago. The Editor and Publisher apologize for any distress this error may have caused.

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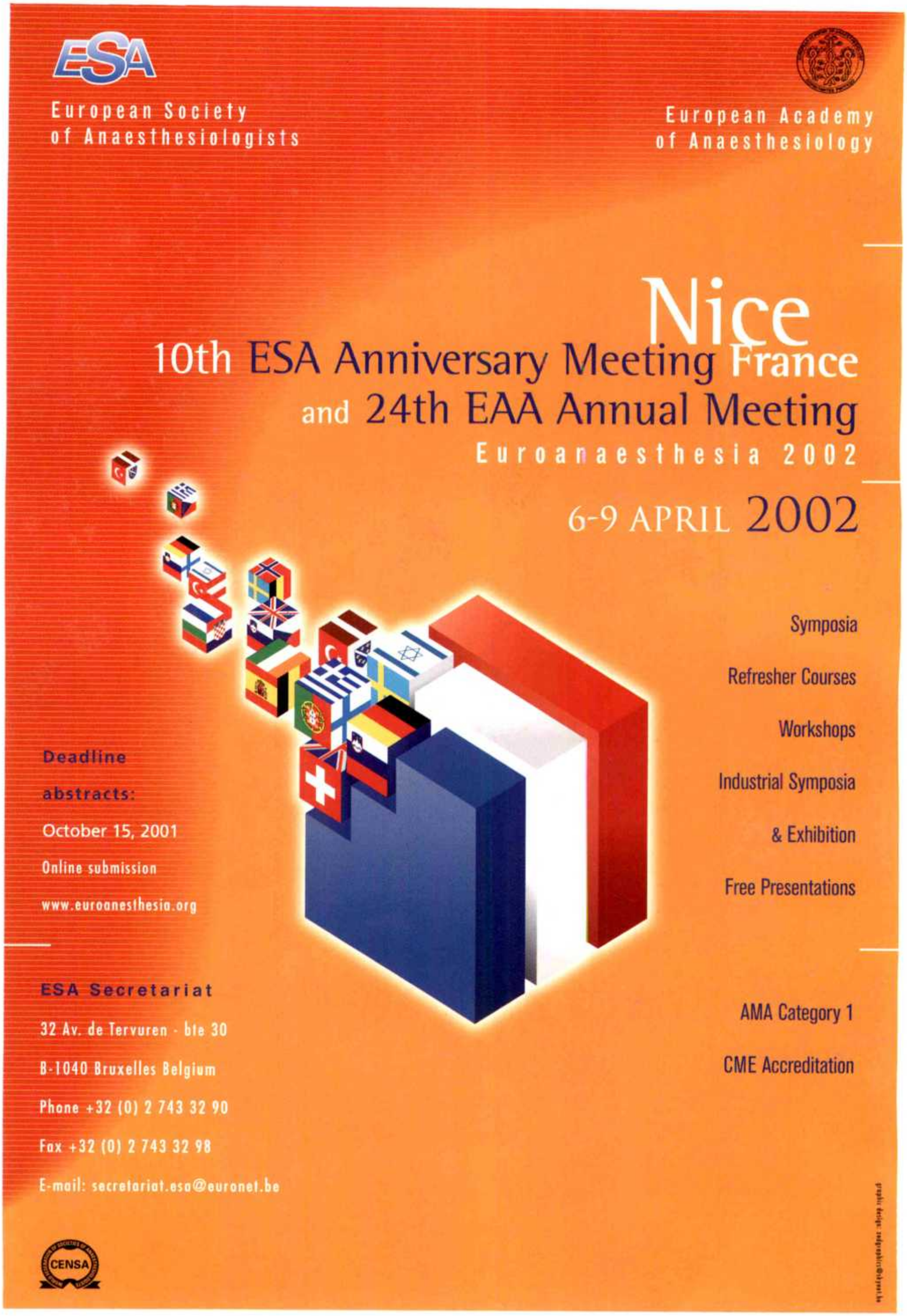

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(rofecoxib)

ABRIDGED PRODUCT INFORMATION

Refer to Summary of Product Characteristics before prescribing

PRESENTATION

Tablets: 25 mg and 50 mg tablets each containing 25 mg or 50 mg of rofecoxib.

USES

Relief of acute pain. Treatment of primary dysmenorrhoea.

DOSAGE AND ADMINISTRATION

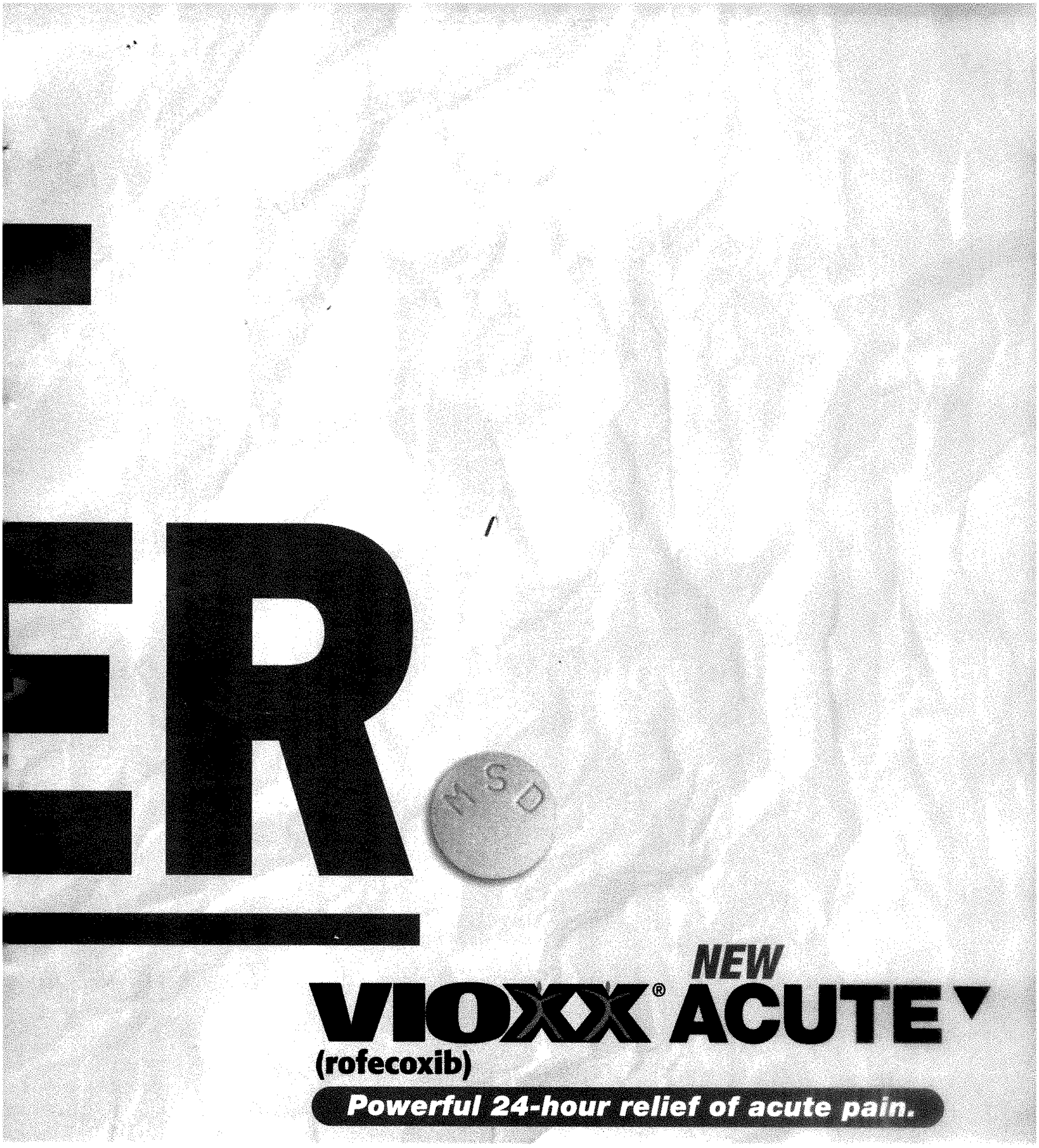
The recommended adult initial dose is 50 mg once daily, orally, with or without food. Subsequent doses should be 25 or 50 mg once daily. The maximum recommended daily dose is 50 mg. Use for the acute symptomatic period only. *Elderly:* It is prudent to use the lowest recommended dose and exercise caution in the treatment of elderly patients. *Renal insufficiency:* no dosage adjustment is necessary for patients with creatinine clearance 30-80 ml/min. *Children:* not indicated.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Hepatic dysfunction. Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs. Third trimester of pregnancy and lactation. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib. Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension. Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib. Rofecoxib may mask fever. Use of rofecoxib is not recommended in women attempting to conceive. In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB. At chronic daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased. Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib. Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated. *Interactions (pharmacodynamic): Warfarin:* closely monitor the prothrombin time INR when therapy with
rofecoxib is initiated or changed in patients receiving warfarin or similar agents, particu
first few days. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benaze
to 40 mg daily for four weeks to patients with hypertension was associated with a small
of the antihypertensive effect compared to the ACE inhibitor alone. This should be co
patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* c
use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics ar
effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once daily had no effect
platelet activity of low-dose (81 mg once daily) aspirin. Avoid concomitant administration c
with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal fu
rofecoxib and either cyclosporin or tacrolimus is used in combination. *Interactions (pharm*
Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* conside
monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are ac
concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rof
drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine an
Midazolam: a modest 30% reduction of the AUC of midazolam was seen with rofecoxib
most likely due to increased first pass metabolism through induction of intestinal CYP3
by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4
pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be a
clinically significant extent. However exercise care when co-prescribing substrates of C



Rifampicin: co-administration of rofecoxib with rifampicin, a potent inducer of CYP roduced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, e highest dose when rofecoxib is used with potent inducers of hepatic metabolism. Based data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.

Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis fecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib be used during the first two trimesters of pregnancy unless the benefit to the patient he risk to the foetus. *Lactation:* contra-indicated.

ECTS

ng drug-related undesirable effects were reported at an incidence greater than 1% and placebo in analgesia clinical studies in patients treated with rofecoxib 50 mg or 25 mg ys: dizziness, diarrhoea, diaphoresis, dyspepsia. The following drug-related undesirable reported at an incidence greater than placebo in osteoarthritis clinical studies in patients rofecoxib 12.5 mg or 25 mg for up to six months, or in post-marketing experience. *≥1/100, <1/10); Uncommon (≥1/1000, <1/100); Rare (≥1/10,000, <1/1000); Very ,000) and isolated cases]*

hole/site unspecified: *Common:* oedema/fluid retention, abdominal pain, dizziness. asthenia/fatigue, abdominal distension, chest pain. *Very rare:* hypersensitivity reactions, gioedema, urticaria and anaphylactic/ anaphylactoid reactions. ***Blood and the lymphatic system disorders:*** *Common:* haematocrit decreased. *Uncommon:* haemoglobin decreased, erythrocytes decreased, leukocytes decreased. *Very rare:* thrombocytopenia. ***Cardiovascular system:*** *Common:* hypertension. *Very rare:* congestive heart failure. ***Digestive system:*** *Common:* heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia. *Uncommon:* constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux. *Rare:* peptic ulcers, gastro-intestinal perforation and bleeding (mainly in elderly patients), gastritis. ***Hepatobiliary disorders:*** *Common:* alanine aminotransferase increased, aspartate aminotransferase increased. *Uncommon:* alkaline phosphatase increased. *Isolated cases:* hepatotoxicity including hepatitis and jaundice. ***Eyes, ears, nose and throat:*** *Uncommon:* tinnitus. *Very rare:* blurred vision. ***Metabolism and nutrition:*** *Uncommon:* weight gain. ***Musculoskeletal:*** *Uncommon:* muscular cramp. ***Nervous system:*** *Common:* headache. *Uncommon:* insomnia, somnolence, vertigo. *Very rare:* paraesthesia. *Isolated cases:* aseptic meningitis. ***Psychiatric disorder:*** *Uncommon:* depression, mental acuity decreased. *Very rare:* confusion, hallucinations. ***Respiratory system:*** *Uncommon:* dyspnoea. *Very rare:* bronchospasm. ***Urogenital:*** *Uncommon:* BUN increased, serum creatinine increased, proteinuria. *Very rare:* renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy. ***Skin and skin appendages:*** *Common:* pruritus. *Uncommon:* rash, atopic dermatitis. *Very rare:* alopecia. *Isolated cases:* cutaneo-mucosal adverse effects and severe skin reactions including Stevens-Johnson Syndrome. In clinical studies, the undesirable effects profile was similar in patients treated with rofecoxib for one year or longer. The following serious adverse effects have been reported in association with the use of NSAIDs and cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome, hepatotoxicity including hepatic failure.

PACKAGE QUANTITIES AND BASIC NHS COST

25 mg: packs of 14 tablets: £10.79. 50 mg: packs of 7 tablets £[illegible].39
Marketing Authorisation numbers: Tablet 25 mg PL 0025/0408 Tablet 50 mg PL 0025/0409
Marketing Authorisation holder: Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

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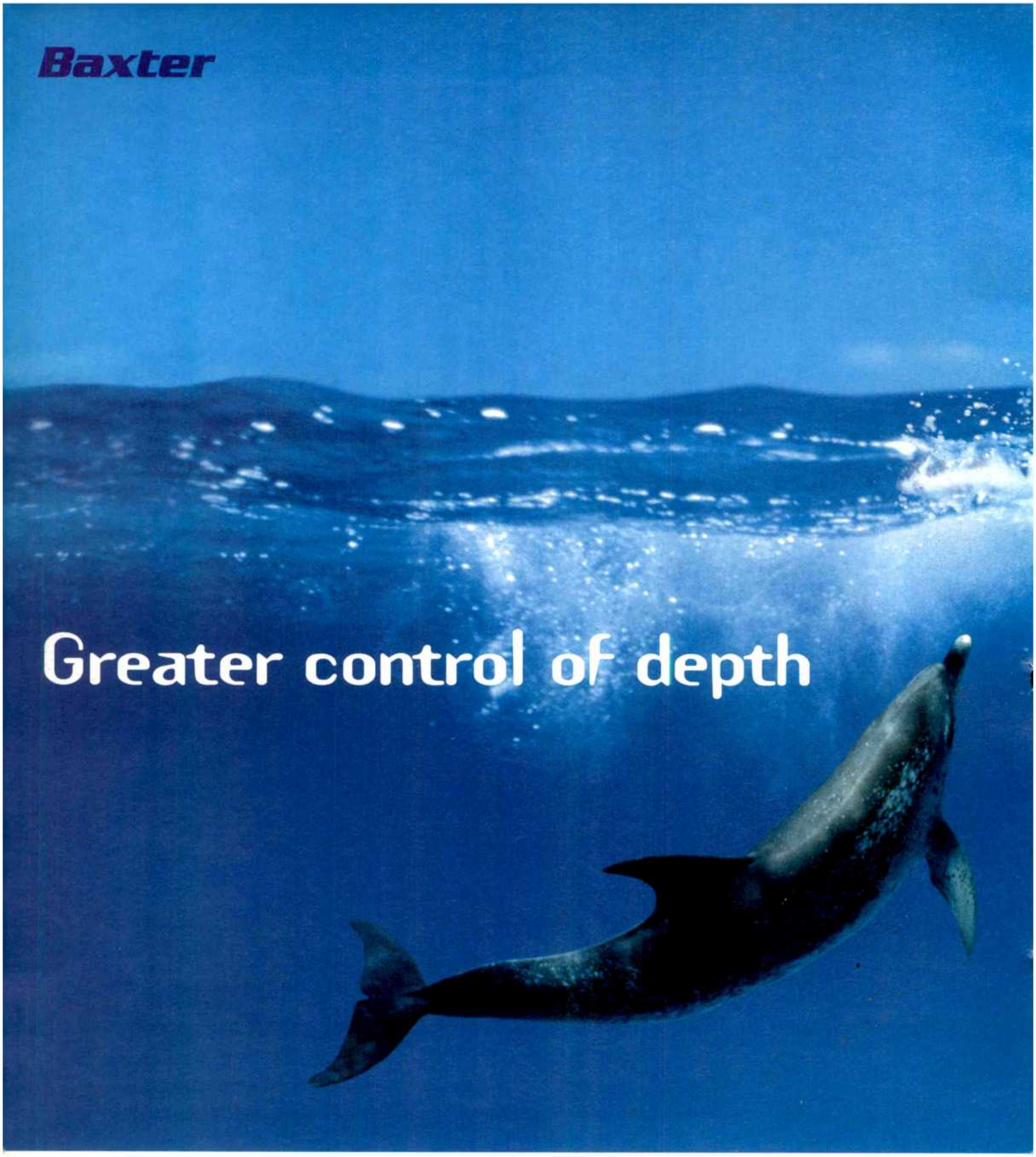
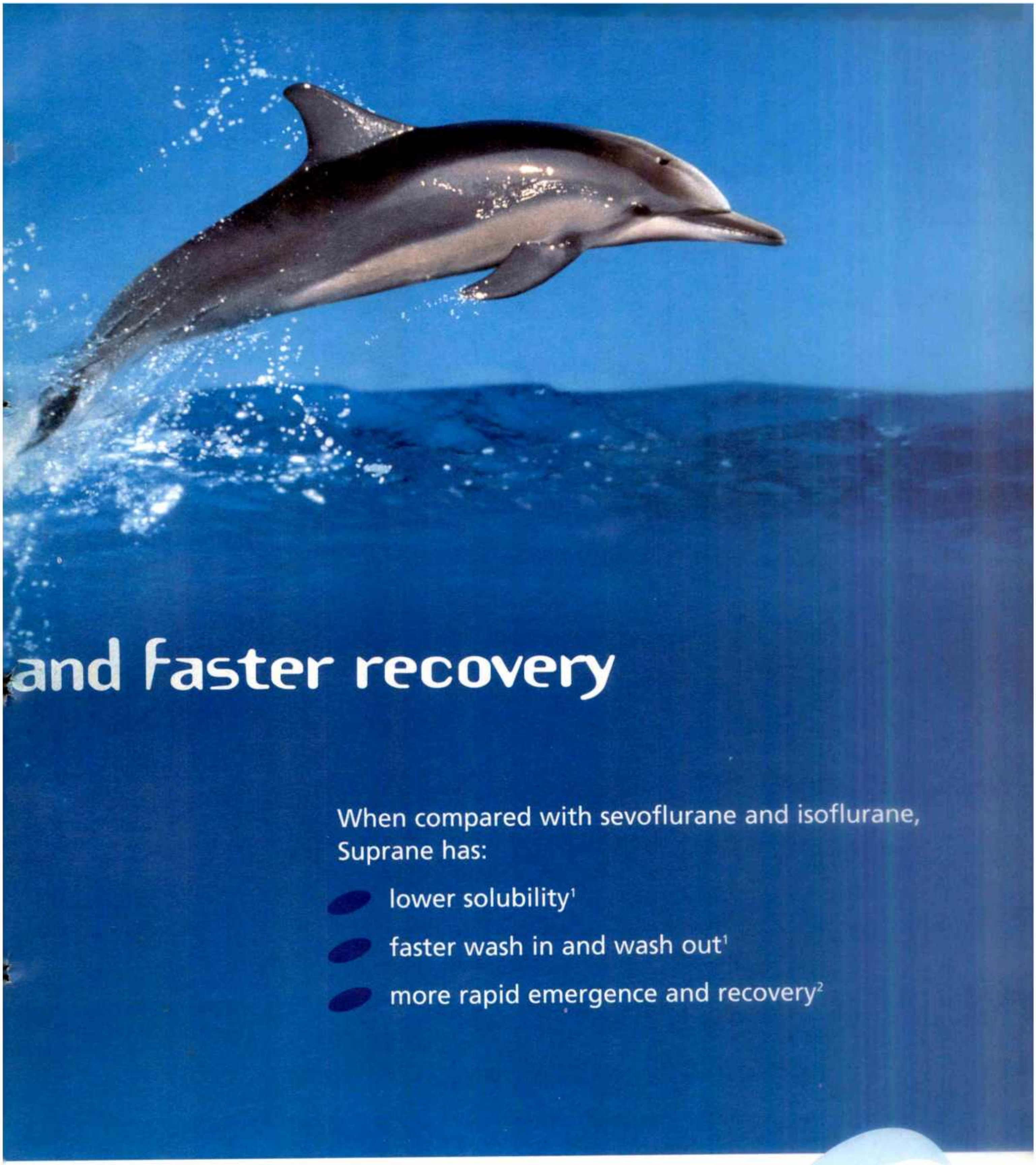


SUPRANE® (desflurane) PRESCRIBING INFORMATION **Presentation:** Amber glass bottle containing 240ml desflurane, supplied as pure drug substance. Suprane is a volatile liquid for administration by inhalation. Store in an upright position at room temperature (25°C). **Indication:** Inhalation agent for induction and/or, maintenance of anaesthesia for inpatient and outpatient surgery in adults and maintenance of anaesthesia for inpatient and outpatient paediatric surgery. **Dosage:** Suprane should be administered by trained anaesthetists using a specific vaporiser designed for Suprane. MAC is age-specific and decreases with increasing age. *Induction.* Inspired concentrations of 4-11% of Suprane usually produce surgical anaesthesia in 2-4 minutes. Suprane is not recommended for paediatric induction. *Maintenance.* Surgical anaesthesia may be sustained with 2-6% Suprane when nitrous oxide is used concomitantly. Suprane at 2.5-8.5% may be required when administered using oxygen or oxygen enriched air. Concentrations of up to 18% Suprane have been administered for short periods of time, but if high concentrations are used with nitrous oxide, ensure that the inspired mixture contains a minimum of 25% oxygen. Concentrations of 1-4% in nitrous oxide/oxygen have been used successfully in patients with chronic renal/hepatic impairment. **Contraindications:** Suprane should not be used in patients in whom general anaesthesia is contraindicated, in patients with known hypersensitivity to halogenated agents, or in patients with known or genetic susceptibility to malignant hyperthermia. Suprane should not be used for induction in patients at risk of coronary artery disease or where increases in heart rate or blood pressure are undesirable. **Precautions:** Suprane is not recommended for paediatric induction, or for use in neurosurgical patients. Suprane may increase CSF or intracranial pressure in patients with space occupying lesions. A lower concentration is recommended for hypovolaemic, hypotensive and debilitated patients. Sensitivity hepatitis may be caused in patients previously sensitised by exposure to other halogenated anaesthetics. Suprane has been shown to trigger malignant hyperthermia. To minimise the risk of formation of carbon monoxide in rebreathing circuits, carbon dioxide absorbents should not be allowed to dry out. Suprane is not indicated during pregnancy or breas



When compared with sevoflurane and isoflurane, Suprane has:

- lower solubility[1]
- faster wash in and wash out[1]
- more rapid emergence and recovery[2]

feeding. **Side effects:** Suprane may cause dose-dependent cardio-respiratory depression. Nausea and vomiting have been observed. Hepatitis may occur in patients sensitised by prior exposure to halogenated anaesthetics. In adult induction, cough, breath holding, laryngospasm, apnoea and salivation have been reported. Transient elevations in white blood cell count have been observed. Rare cases of malignant hyperthermia have been reported. No information exists on the effects of Suprane on the ability to drive or operate machinery. An adequate period, at least 24 hours, is needed to ensure full recovery. **Interactions:** Suprane potentiates commonly used muscle relaxants. Lower doses of Suprane are required in those receiving opioids, benzodiazepines, other sedatives, and nitrous oxide. **Overdose:** There is no experience of overdose in humans. Please consult Summary of Product Characteristics for recommendations in the case of overdosing. **Legal category:** POM. **Packs:** Suprane 240ml in amber glass bottles. **Basic NHS price:** £44.41 per bottle. **PL number:** 0116/0327. **PL holder:** Baxter Healthcare Ltd., Caxton Way, Thetford, Norfolk IP24 3SE. **Date of preparation:** December 1999.

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References: 1. Eger E I. Anesth. Review. 1993;**20**:87-92. 2. Dupont I et al. Br J Anaesth. 1999;**82**:355-359.

Baxter Healthcare Ltd., Wallingford Road, Compton, Nr. Newbury, Berkshire. RG20 7QW. Tel: 01635 206000

Suprane®
desflurane

Precise control in
maintenance anaesthesia

SUP021/UK/0200

EPREX® ABBREVIATED PRESCRIBING INFORMATION

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use; increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM.

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*Haemoglobin levels >10 to ≤13 g/dL.

References:

1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz MC. *Orthopedics.* 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

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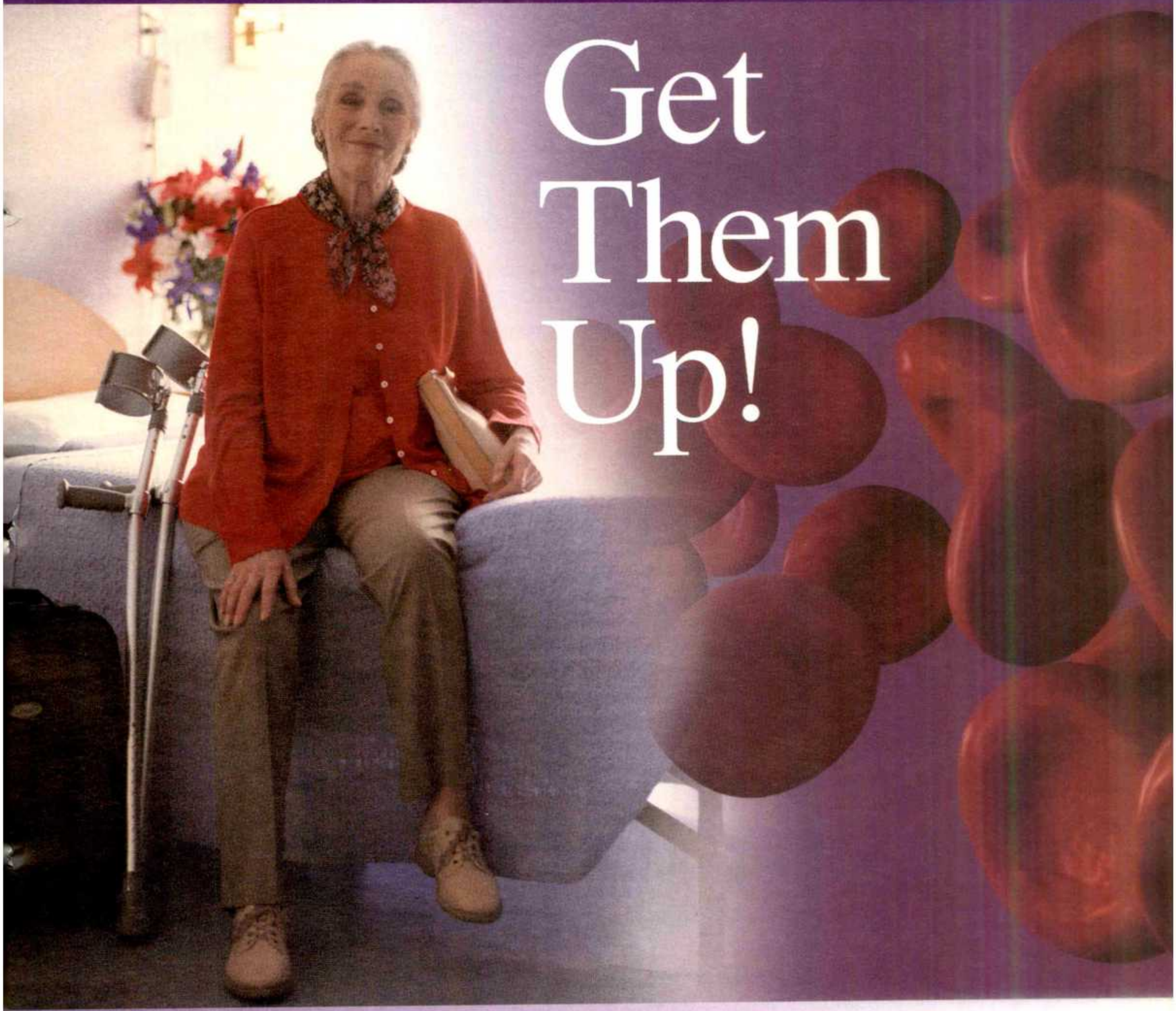

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From January 2002, the Summary of all Clinical Investigations, Laboratory Investigations and Short Communications (but not Reviews, Case Reports or Commentaries) published in the *British Journal of Anaesthesia* will be structured under the headings:

Background
Methods
Results
Conclusions

All new manuscripts submitted to the *British Journal of Anaesthesia* from 1 May, 2001 should therefore be presented in this format. If an Editor asks for a revised version of a previously submitted manuscript, please change the Summary in your next draft to the new structured format.

Jennifer M. Hunter
Editor-in-Chief

$500,000 IARS Frontiers in Anesthesia Research Award—Fourth Recipient

The Board of Trustees of the International Anesthesia Research Society (IARS) announced at the 75th Clinical and Scientific Congress the fourth recipient of the $500,000 IARS Frontiers in Anesthesia Research Award. The award was established by the IARS in 1994 'to foster innovation and creativity by an individual scientist in the field of Anesthesiology'. The fourth recipient is:
Mark A. Schumacher, PhD, MD, University of California, San Francisco, California.

Dr Schumacher's research project is titled 'Stretch-Inactivated Channels in Pain Transduction'. Dr Schumacher is an Assistant Professor in the Department of Anesthesia and Perioperative Care at the School of Medicine, University of California, San Francisco.

Forthcoming Institute for International Research Pharmaceutical Event: Achieving a Balance between Meeting Regulatory and Pharmacopoeial Harmonization

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Final FRCA Revision Course

Leicester, UK, October 2–5, 2001

An intensive revision course for the Final FRCA based on small group tutorials and including written and oral examination practice will be held at Leicester Royal Infirmary. Fees: £290 non-residential (including lunch and refreshments); £390 residential (including lunch and refreshments). Course director is Dr Jonathan Thompson. Places are strictly limited. Please telephone Christine Gethins on +44 (0) 116 258 5291 (anae@le.ac.uk) for a booking form.

Dingle 2001—3rd Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 3–7, 2001

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

4th SW Thames Anaesthesia Forum

Da Balaia, The Algarve, Portugal, October 8–11, 2001

The scientific programme will include lectures and discussions on: Acute and Chronic Pain; Paediatric Update; Obstetric Anaesthesia; Neurology and Anaesthesia; ITU and Relevant Medical Topics; Cardiothoracic Anaesthesia; Day Case Surgery; Regional Blocks; New Drugs Update; Training and Education; Information Technology; Free Papers. New! Core Topics for your Personal Portfolio. Guest Speakers, Videos on new Drugs, Equipment and Techniques.

Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: September 1, 2001. Meeting approved for CEPD.

For full information and to secure a place, please visit: www.anaesthesiaupdates.com or contact: Dr J. B. Liban, Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT. Tel: +44 (0) 208725 0018; Fax: +44 (0) 208725 3135; E-mail: liban@mailbox.co.uk

Annual Meeting of the International Society for Anaesthetic Pharmacology (ISAP) (formerly SIVA)

New Orleans, Louisiana, October 12, 2001

For further information contact: International Society for Anaesthetic Pharmacology (ISAP), 2 Summit Park Drive, Suite 140, Cleveland, OH 44131-2553, USA.Tel: +1 216 447 7862; Fax: +1 216 642 1127; E-mail: larshq@iars.org; Web address: www.isaponline.org

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The Royal College of Anaesthetists Senior Fellows Club Inaugural Meeting

Royal College of Anaesthetists, Thursday, October 24, 2001 (11.30–14.00)

Speaker: Dr John Nunn 'Climate change and extinction'

This meeting is open to anyone retired from full-time anaesthetic practice who has been associated with the college. The president will give a brief summary of current collegiate activities. Cost £15 to cover buffet lunch and drinks. Places are limited.

Apply to Mrs Mandie Kelly, The Royal College of Anaesthetists, 48/49 Russell Square, London WC1B 4JY, UK.

Tel: +44 (0)20 7813 1900. Fax: +44 (0)20 7813 1876. E-mail: mkelly@rcoa.ac.uk

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

ENT Anaesthesia

London, UK, November 1–2, 2001

A limited number of places are available on a course organized by Dr Ariel Patel and Dr Catrion Ferguson for Institute of Laryngology and Otology, Royal Free and University College Medical School and Royal National Throat, Nose and Ear Hospital.

For further information,please contact: Joy Gibney or Charmaine Henry, Administration, Institute of Laryngology and Otology, 330-336 Grays Inn Road, London WC1X 8EE, UK. Tel: +44 (0)20 7915 1514/92; Fax:+44 (0)20 7837 9279. E-mail: j.gibney@ucl.ac.uk/c.henry@ucl.ac.uk

5th Annual Conference of the Indian Association of Cardiovascular and Thoracic Anaesthesiologists

Bangalore, India, November 2–4, 2001

It is hoped that there will be a CMF in cardiac anaesthesia on one day preceding the conference, for the benefit of the postgraduate students.

For further information, please contact: Dr Suresh K. Ghaste, Organising Secretary, VIACTA Conference, Professor and Head of Department of Anaesthesiology, Sri Jayadeva Institute of Cardiology, M. H. Complex, Bangalore, S60 002, India. Tel: + 0 6707575 Ex. 138, E-mail: skghaste@yahoo.com

European One Day Course in Spinal Endoscopy

Bradford Royal Infirmary, England, November 9, 2001

This course will be of interest to all those involved with central neural blocks and especially to those involved with the investigation and management of patients with back and radicular pain.

For further information and to secure a place please contact: Dr J. Richardson, MERIT Centre, Bradford Royal Infirmary, Bradford BD9 6RJ, England. Tel: +44 (0) 1274 364271; Fax: +44 (0) 1274 366811

International Scientific Meeting to celebrate the retirement of Professor R. S. Jones OBE, after 40 years in Veterinary Anaesthesia

The Racecourse, Chester, UK, December 6–7, 2001

Theme for the first day: 'Forty Years of Veterinary Anaesthesia'.
Theme for the second day: 'One Vet's Multidisciplinary Contributions'.

For further details please contact: Professor J. M. Hunter. Tel: +44 (0)151 706 4008; Fax: +44 (0)151 706 5884; E-mail: jwa@liv.ac.uk

3rd National Conference Indian Society of Neuroanaesthesiology and Critical Care (ISNACC-2002)

Mumbal, India, January 12–13, 2002

For further details contact: Dr (Mrs) Kanchan S. Jagger, Room No. 423, 4th Floor, Department of Anaesthesia, L.T.M. Medical College Sion, Mumbal: 400022, India. Tel: +91 22 4022976 (O), +91 22 4371811 (R); Fax: +91 22 4076100; Email: kanchanjagger@yahoo.co.uk or isnacc2002@sify.com

20th Annual Symposium Clinical Update in Anaesthesiology and Advances in Techniques of Cardiopulmonary Bypass

Paradise Island, Bahamas, January 13–19, 2002

Abstract, Poster and Free Papers Information: (**Deadline – November 1, 2001**) Helen Phillips, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1010, New York, NY 10029-6574, USA. Tel: +1 212 241 7467; Fax: +1 212 426 2009; E-mail: helen.phillips@mssm.edu

Welcome to the second Euro-PNB winter symposium!

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Full participation certifies 15 Eu CME points. Fee: 250.-CHF. Places are limited to 40 delegates.

Registration before December 1, 2001 to: Assoc. Prof. Alain Borgeat, Head of Anaesthesia and Intensive Care, Orthopedic University Clinic, Balgrist/Zürich, Forchstrasse 340, CH-8008 Zürich, Switzerland.
Tel: +41 1 386 38 32; Fax: +41 1 386 16 09; E-mail: aborgeat@balgrist.unizh.ch

13th SW Thames Anaesthesia Update

Belle Plagne, French Alps, January 28–February 1, 2002

The scientific programme will include lectures and discussions on: Acute and Chronic Pain; Paediatric Update; Obstetric Anaesthesia; Neurology and Anaesthesia; ITU and Relevant Medical Topics; Cardiothoracic Anaesthesia; Day Case Surgery; Regional Blocks; New Drugs Update; Training and Education; Information Technology; Free Papers. Case Presentation Competition. Guest Speakers, Workshops, Videos on new Drugs, Equipment and Techniques.

Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: December 10, 2001. Meeting approved for CEPD.

For full information and to secure a place please contact: Dr J. B. Liban, Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT. Tel: +44 (0) 208725 0018; Fax: +44 (0) 208725 3135; E-mail: liban@mailbox. co.uk; Website: www.anaesthesiaupdates.com

International Anaesthesia Research Society Annual Clinical and Scientific Congresses

March 16–20, 2002
IARS 76th Clinical and Scientific Congress, San Diego Marriott Hotel & Marina, San Diego, California, USA.

March 22–26, 2003
IARS 77th Clinical and Scientific Congress, New Orleans Marriott, New Orleans, Louisiana, USA.

March 27–31, 2004
IARS 78th Clinical and Scientific Congress, Tampa Marriott Waterside Hotel, Tampa, Florida, USA.

March 11–15, 2005
IARS 79th Clinical and Scientific Congress, Hilton Hawaiian Village, Honolulu, Hawaii, USA.

Contact information: IARS, 2 Summit Park Drive, Suite 140, Cleveland, OH 44131, USA. Tel: +1 216 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Web: www.iars.org

Putting New Flesh on Old Bones: a major conference on Issues in the Perioperative Care of Geriatric Trauma

The Netherwood Hotel, Grange-Over-Sands, UK, May 10, 2002

Speakers include: Nigel Sharrock (New York); Martyn Parker (Peterborough)

Deadline for free paper abstracts: February 1, 2002.

Please contact Dr Andrew Severn for details: Tel: +44 (0)1524 583517; Fax: +44 (0)1524 583519.

Australian and New Zealand College of Anaesthetists Annual Meeting

Brisbane Convention and Exhibition Centre, Brisbane, Australia, May 11–15, 2002

For further information please contact:

ANZCA 2002 Secretariat, PO Box 1280, Milton QLD 4064, Australia.

Tel: +61 (0) 7 3858 5537; Fax: +61 (0) 7 3858 5510;
E-mail: anzca2002@im.com.au; Website: www.anzca.edu.au

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Anaesthesia outside the square: CECANZ Conference 2002

Christchurch, New Zealand, September 18–20, 2002
For information, please contact: Conference Secretariat Joy Mehlhopt, Conference Innovators, P.O. Box 1370, Christchurch, New Zealand.

Tel: +61 3 379 0390; Fax: +61 3 379 0460; E-mail: joy@conference.co.nz. Website: www.cecanz2002.org.nz

Société Française d'Anesthésie et de Réanimation

Annual congresses will take place in Palais des Congrés, Porte Maillot, Paris on the following dates:

September 26–29, 2002
September 18–21, 2003
September 20–October 3, 2004
September 29–October 2, 2005

For further information, please contact: SFAR, 74, rue Raynouard, F-75016 Paris, France. Tel: +33 1 45 25 82 25; Fax: +33 1 40 50 35 22; E-mail SFAR@invivo.edu

Dingle 2002—4th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 2–6, 2002

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

Australian Society of Anaesthetists National Scientific Congress

Adelaide, Australia, October 26–30, 2002

This is the Society's premier scientific conference, held in an interesting part of the world.

For further details, please contact: Festival City Conventions, P.O. Box 949, Kent Town, S.A. 5071, Australia. Tel: +61 (0)8 8363 1307; Fax: +61 (0)8 8363 1604: E-mail: asa2002@fccconventions.com.au

8th International Congress of Cardiothoracic and Vascular Anesthesia
19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:
8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel
Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H.Rosenberg, Helsinki University Hospital, Helsinki FIN00029 HUS, Finland.

E-mail: per.rosenberg@hus.fi
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Web address: www.congrex.fi

Dingle 2003—5th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 1–5, 2003

For further information contact:

Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

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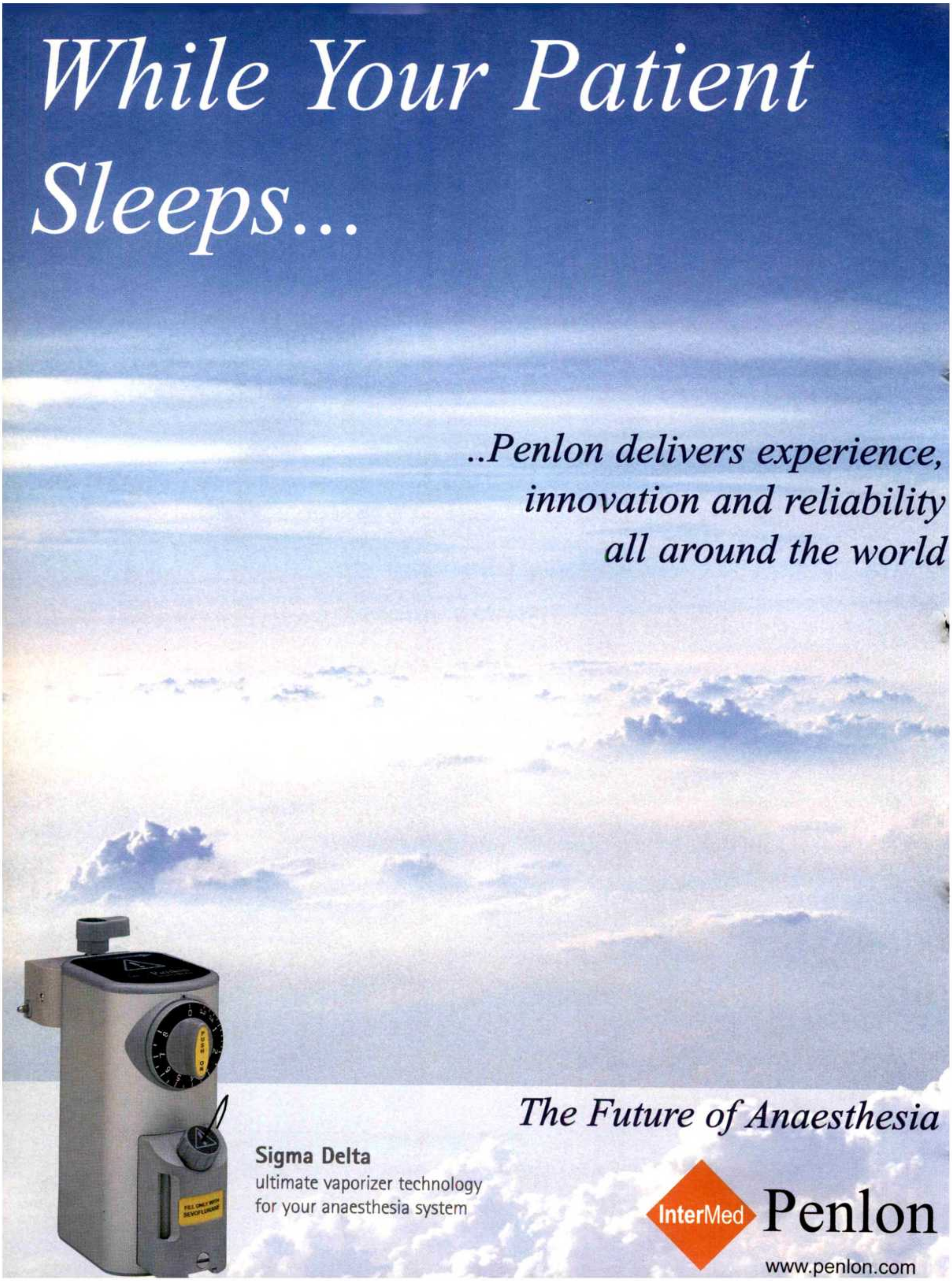

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Journal of the International Anesthesia Research Society, the Society of Cardiovascular Anesthesiologists, the Society for Pediatric Anesthesia, the Society for Ambulatory Anesthesia, the International Society for Anaesthetic Pharmacology, and the Society for Technology in Anesthesia

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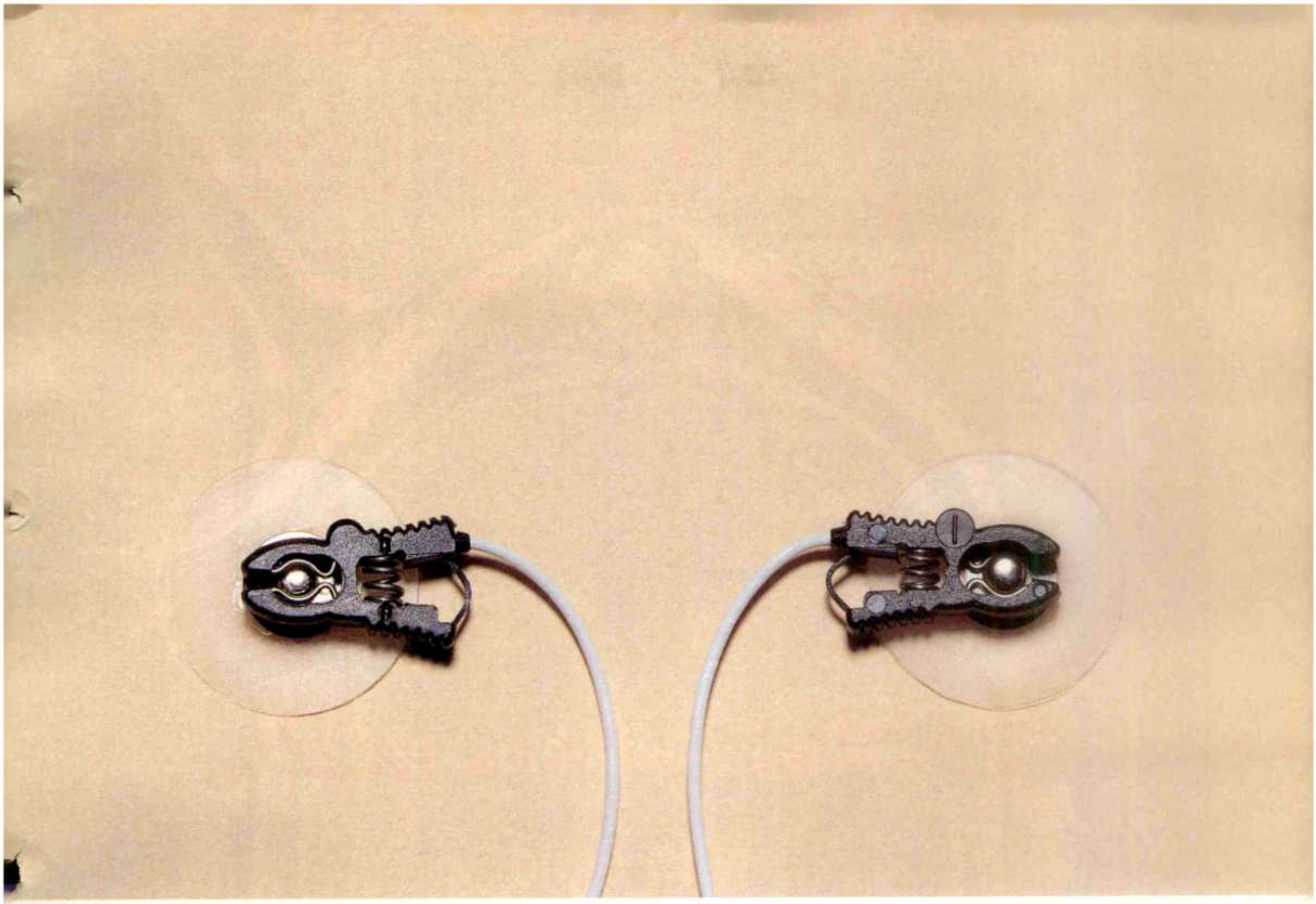

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BRITISH JOURNAL OF ANAESTHESIA

Volume 87, Number 4, October 2001

Editorial I

Measuring the outcome of surgical procedures: what are the challenges?

Hall and colleagues[1] have presented an interesting study linking a number of physiological variables to outcomes in persons who have undergone hip arthroplasty. Presumably, the motivation for the study was to identify strategies to reduce the perioperative stress response, which would in turn aid recovery.

Essentially this study found that there was a relationship between the inflammatory response, as measured by interleukin 6 (IL-6) and the number of postoperative days before patients could walk 10 and 25 m independently. Outcomes 1 and 6 months after surgery, as measured by the WOMAC (a self-report pain and activity questionnaire with excellent psychometric properties), were not influenced by any of the physiological variables measured in the study. The endocrine response did not appear to influence either the short-term or the long-term outcome.

A question comes to mind in interpreting these findings. Is there a biological reason for suspecting that any of the postoperative physiological variables could have enduring effects such that they might influence walking and activity?

There is supporting evidence that surgical procedures necessitating extensive tissue damage produce a greater inflammatory response.[2] For example, in the 11 studies comparing open with laparoscopic cholecystectomy, summarized recently by Kehlet,[3] the lower inflammatory response in the laparoscopic group was associated with shorter length of hospital stay.

Length of stay in hospital, however, is not necessarily the best indicator of recovery. This measure is influenced by the health-care system and the administrative culture in which the patient and physician function, as well as by the patient's expectation of hospital stay and the availability of community and family postoperative support. In other words, administrative end-points such as the length of stay are influenced by many factors outside the investigator's control. Thus, an investigator may be unwise to rely solely on these outcomes, however attractive they may be from an administrative point of view. With length of stay as the only outcome, there is the risk of a study finding no effect when there is one, or of wrongly assuming the patient had recovered just because he or she had been discharged from the hospital.

Clearly, if the interest is in measuring recovery after surgery, it would be best to pick a measure of this desirable outcome. This was the dilemma that Hall and colleagues encountered in their study, because, as they point out, there are no accepted and validated measures of postoperative recovery.

As a proxy measure of recovery, they chose the number of days it took patients to walk 10 and 25 m.[4] This measure has face validity (makes sense) for recovery, but it may not satisfy another desirable property of an outcome measure, namely being independent of outside influences. Many factors could delay the day on which a patient walked a target distance. Perhaps a test was scheduled, a family crisis intervened, or the physiotherapist was absent. Notwithstanding factors outside the investigators' control, time-to-event data have statistical features that make them more complex to analyse and interpret. Statistically speaking, the data are discrete and ordinal (i.e. 1, 2 or 3). The problem is that much valuable information on the patient's ability to walk is not incorporated in this crude measure. Loss of information introduces misclassification such that like and unalike can be grouped together and like and like can be separated.

For example, consider that a person who walks 6 m four times a day for the first 3 days and then the targeted 10 m on day 4 (24 m × 3 days) would be classified the same as someone walking not at all for 3 days and then walking the full 10 m once on day 4.

When misclassification is random, i.e. it is unrelated to the exposure (to IL-6 in this study), then only noise is introduced, making it more difficult to detect an association. In this study, there may be concern that non-random misclassification (systematic error) would have crept in if persons with a lower inflammatory response had been able to walk a slightly longer distance or more frequently during the day, but did not necessarily achieve the target distance any earlier. If this is true, the result is a biased estimate of the effect of inflammatory response on recovery of walking and the bias is towards the null hypothesis, underestimating the effect of IL-6 on recovery. As there were many 'non-associations' in this paper, particularly with respect to endocrine responses, questions arise as to whether these

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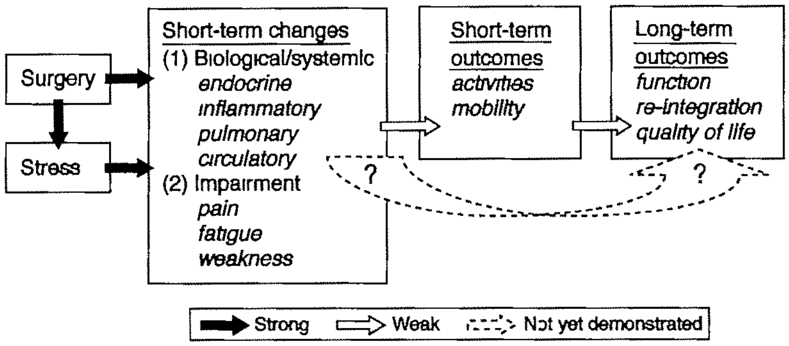

Fig 1 A model for measuring the outcome of surgical procedures.

were true negatives or false negatives introduced by non-random misclassification.

So what is an optimal measurement strategy for interventions that have important physiological and patient effects? Clearly, the outcome must be biologically related to the intervention and should not be influenced by extraneous factors. Moreover, information should not be lost because of imprecision of the measure. Ideally, the precision of the measurement should be close to the biological precision of the underlying construct. Walking ability is not measured on a 'yes/no' scale. It is a complex construct influenced by strength, range of motion, balance and the presence of pain, and can be assessed in terms of stride length, distance covered, time and degree of assistance. In the study of Hall and colleagues, the exposure variables (inflammatory and endocrine variables) were measured with great accuracy; however, the measure of outcome was not subjected to the same precision. As a general rule, outcome should be measured with as much accuracy as is biologically possible.

What are the measures that are biologically related to recovery after total hip replacement in the short term and in the long term? Postoperative mobility is an appropriate construct reflecting not only hip-related function but also general condition. Walking is one measure of mobility, but the concepts of distance, speed, endurance and pain need to be incorporated. For example, measures such as gait speed,[5] 2- or 6-min walks,[6 7] the timed Up-and-Go test[8] and total distance walked per day are more precise measures of walking, and are not difficult to incorporate into routine clinical practice and research.

While the WOMAC is considered an excellent measure of health status for people with osteoarthritis of the hip or knee,[9] the areas covered in the WOMAC may not be directly influenced by the physiological variables measured in the hours and days after surgery. Rather, the link may be through an intermediate outcome such as mobility. It is more likely that a study would show an association between two variables that have a direct biological link than between two variables that are more loosely connected.

Mobility is just as relevant a measure 1 and 6 months after hip replacement as it is postoperatively. The WOMAC captures mobility but also taps other constructs, such as emotional well-being and social participation, which are connected to postoperative variables more remotely and are also influenced by outside elements. In the long term, measures of community mobility are particularly relevant and are associated with overall health status and quality of life. A test such as the 6-min walk,[7] a measure of functional exercise capacity, is attractive as it is measured objectively with a standardized protocol (distance covered in 6 min); its influencing variables (effort and practice) are known; it is measured on a continuous scale, which makes statistical analyses simpler yet more powerful; and it has a natural zero point when an individual is unable to walk, thus eliminating the problem of what to do with people with limited walking ability. The test also has age and sex norms.

In the design of studies of surgical outcomes, it could be proposed that the measurement strategy should consider the link between biology and outcome, the influence of other variables on the chosen outcome, and the statistical properties of the measures. Clearly, the timing of the measurement must also reflect the time course of recovery, which would differ by type of surgery. For example, for hip arthroplasty, 6 months is a relevant time point, whereas for abdominal surgery 6 weeks may be more appropriate.

In choosing a measurement strategy, it is helpful to consider how the various parameters that could be studied influence each other and what are the likely causal pathways. We propose the simple model depicted in Figure 1. It is well known that surgery is a stressor and that both the surgery and the associated stress produce immediate biological changes that can be measured in the perioperative period. These changes are physiological and systemic. In our model, we have depicted these strong relationships with solid arrows. It is biologically plausible that these short-term physiological effects have an impact on short-term function. Hall and colleagues studied this association and provided some evidence of a relationship, but the evidence was weakened by a less than optimal choice of outcome. Further study of this association would be important. Hall and colleagues did not find any relationship between the short- and long-term outcomes.

At the moment, we cannot tell whether the lack of association was because of the selected short-term outcomes (the long-term outcome measure was ideal) or because there is no biological reason for an association in the context of hip arthroplasty. The open arrows indicate that an association has not yet been shown. There was also no association between short-term biological changes and the long-term outcome. We suggest that there is no true association, except through short-term effects, and we have depicted our hypothesis with a dashed arrow. Therefore, in our model we have placed short-term outcomes as an intermediary between biological changes and long-term outcomes. Clearly, more research on these pathways is needed, particularly if interventions can be devised to improve outcome in both the short and the long term.

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Editorial II

Time to light the grey touchpaper! The challenge of anaesthesia in the elderly

New ideas, although they may sound as though they are the logical consequences of progress, are often found to be based on past experience. Hindsight is always a factor driving innovation. In the last few years we have seen major changes in the way our profession trains, maintains standards and plans the delivery of services. Paediatric anaesthesia, for example, has developed in response to alleged shortcomings in the services that were delivered to a unique group of patients. The profession has taken time to accept these truths, but it has ultimately conceded. A subspecialty has evolved. Is there a place for such thinking in anaesthesia for the elderly? Recently, Dodds and Allison have challenged the profession for casual acceptance of a troublesome complication in the elderly, postoperative cognitive dysfunction, stating that it 'should attract the same interest in further research that a similar 25% incidence would obtain in a young adult or paediatric group'.[1] To pursue the topic further, it is necessary to ask three questions. First, is there a case for considering that the elderly are 'different' from other adults encountered in anaesthetic practice? Second, is there a deficiency in the service? Third, is study of the elderly patient undergoing anaesthesia worthwhile?

Are elderly patients 'different'?

Priebe distinguishes between age-related physiological cardiovascular changes and age-related pathological cardiovascular disease, and supports the view that the elderly deserve special consideration.[2] In the healthy elderly patient there is a loss of functional reserve that may make the system vulnerable to challenge. Examples are age-related upregulation of sympathetic outflow, with desensitization of beta-receptors and an increasing reliance on the Frank–Starling mechanism for the regulation of cardiac output. These are important physiological changes of clinical relevance. However, it is easy to get distracted into thinking about cardiovascular *pathology* when thinking about the elderly. This may lead to a complacent attitude towards the needs of the healthy elderly patient. It is possible to take a view that the problems of the elderly are the consequence of age-related diseases, and that all that is necessary is an understanding of the disease, an essential prerequisite for any anaesthetist. This view does not support the idea that the elderly are a unique group of patients. To some extent this is the view taken in an article in this issue: Jin and Chung discuss the differences between elderly and younger adults with reference to whether complications can be prevented.[3] It is clear from the discussion of the cardiovascular system that some concepts, for example the Goldman risk index, are well established in the collective consciousness of the profession. One is left with the conclusion that even if age were taken as an independent indicator of risk, it would be dwarfed by the risks of age-related cardiovascular disease.

Those who would make the case for elderly patients being special must, therefore, look away from the cardiovascular system for unqualified support. Here Jin and Chung have the answer: the brain.[3] The brain changes with age. The loss of neurones, the reduction of grey matter, the reduction of neurotransmitters and receptors for norepinephrine and dopamine is progressive, physiological and symptomless. The lowered requirement for propofol in the older patient can be explained in pharmacokinetic terms. It can also be explained in pharmacodynamic terms: the aged brain needs less anaesthetic agent.[4 5] The concept of brain aging as a progressive loss which gives no symptoms until a functional reserve is exhausted is attractive, and one which has implications for our understanding of anaesthetic-related morbidity. As far as pathological processes are concerned, we have one model, Parkinson's disease, in which it is said that up to 80% of nigrostriatal neurons can be lost before the disease is clinically apparent.[6]

Could the neurological complications of anaesthesia and surgery in the elderly be a result of an insult on an aging population of neurons, or should they be explained purely in terms of the known pathological processes affecting the cerebral arteries? Control of the cerebral circulation may be important in preventing perioperative stroke, but it would appear that prevention of stroke does not reduce the burden of perioperative cerebral morbidity. According to the International Study into Postoperative Cognitive Dysfunction (ISPOCD), 14% of the over 70s have not returned to baseline mental state functioning 3 months after surgery.[7] Applying our knowledge of cerebrovascular pathology and physiology, doing all the 'right things' to maintain optimal cerebral oxygenation and tight control of the circulation, does not reduce the incidence. If ever evidence were needed that the elderly brain, even that of the otherwise healthy patient, responds 'differently' from the young brain, this observation suffices. The only significant risk factor for 'late postoperative cognitive deficit' seems to be age.

Postoperative cognitive dysfunction is an enigma. The presence of a lucid interval suggests that the origins may lie with neurotransmitter failure that has taken a day or two to become apparent. Alternately, the dysfunction may result from the cumulative stress of hospitalization, trauma, and pain. There is evidence that early postoperative delirium (by this I refer to a common, reversible, and acute phenomenon) results from poorly managed pain rather than as a complication of analgesic administration.[8] There is also evidence that the use of meperidine and long-acting benzodiazepines such as diazepam is associated with delirium in elderly surgical patients.[9] No such correlations are clear when long-term deficit is considered, but a forthcoming ISPOCD study may provide information about minor and day case surgery in an elderly population, that is, a population in which the 'stress' of hospitalization is minimized. Even if drugs are cleared of blame for long-term dysfunction, 'the anaesthetic' may remain a convenient scapegoat (in the same way as it is for postoperative nausea). The fact is that we still do not know what anaesthetic drugs or techniques do to the elderly brain, and in what way their actions are different from their actions in the younger brain. Predictably, spinal anaesthesia, presumably by virtue of the risk of hypotension, may be associated with more cerebrovascular risk in elderly patients with hip fracture.[10] However, as discussed above, overt cerebrovascular incidents are only the tip of the iceberg of cerebral complications. Many elderly patients are 'never quite the same' after surgery. This observation in itself justifies the view that the elderly are a unique group of patients whose anaesthetic-related morbidity cannot be explained in terms of conventional models of age-related disease.

Is there a deficiency in the way the service is delivered?

The 1999 Confidential Enquiry on Perioperative Deaths (CEPOD) reported on 1077 deaths within 30 days of surgery in England and Wales in the over 90 yr age group.[11] Given that there is no control data (from survivors), and that the life expectancy in that age group is only 3.6 (males) and 4.5 yrs (females), it is difficult to know to what extent the results can be blamed on inadequate delivery of services. For all its weaknesses, CEPOD does offer a useful snapshot of current British practice. For example, 90% of the patients who died had an underlying medical disorder but few received shared care between surgeon and a specialist physician in the final illness. As ever, CEPOD is useful mainly for its case reports directing the ways in which management could be improved. The use of large volumes of i.v. fluids is noted in many of the deaths.

Poor application of basic principles of fluid management underlies some of the problems. An article in the *British Medical Journal* was notable for its elevation of a single case report, of an elderly orthopaedic patient who received inappropriate i.v. fluid, to editorial status.[12] It also generated what the editor described as an 'emotional response' in the correspondence columns and electronic responses.[13–15] No firm conclusions were reached, but one was left with an impression that the fluid requirements of seriously ill, elderly surgical patients were poorly understood, and not addressed by experienced surgical staff or others, such as anaesthetists and clinical biochemists, who could provide expert advice. It is not only failures of management that can provoke criticism. Apparent successes can do also. A woman of 113 yrs survived surgical fixation of a fractured shaft of femur (after a delay of several days during which she was not expected to live), and a stay in intensive care, and lived for another 9 months.[16] There was a spirited discussion of the appropriateness of using intensive care resources for a patient who survives wheelchair dependent and confused.[17] The evidence that a low in-hospital mortality can be achieved where there is adequate high dependency care suggests that some of the problems of using intensive care could be avoided by early intervention and close perioperative supervision.[18] The two case reports are similar in that they demonstrate failure of coordinated decision making by experts in surgery and perioperative medicine, something which the authors of CEPOD would have us believe also. There would appear from these reports to be concern that vulnerable elderly patients are not getting the service that the authors of the reports feel is appropriate, and that there is a deficiency in the way the service is delivered.

Is study of the elderly patient undergoing anaesthesia worthwhile?

Conclusions about anaesthesia in the elderly may be made by extrapolation from studies on younger, and healthier, patients. While the study of the younger population may be easier to reconcile with Ethics Committees and has the undoubted benefit of providing a homogeneous group of patients, extrapolation of the results to the elderly has to be done carefully. Ideally the elderly should be considered as a separate group in research, for example in a direct comparison with a younger group.

Specifically with respect to drug doses and the process of aging, the central cholinergic system has come under scrutiny. It is perhaps a reflection of the lack of communication between medical specialties that the risk of causing severe disturbance of cognition with centrally acting anticholinergic drugs has long been known to medical specialists who care for the elderly, but is only now receiving due attention from anaesthetists. Many drugs in common use have antimuscarinic effects and combinations may potentiate this tendency. For example, an elderly patient taking frusemide and prednisolone may have increased risk of cognitive impairment.[19] There is a suggestion that integrity of the cholinergic system is required in the normal mechanism of action of propofol.[20] There has been recent interest in the cholinergic system in the mechanism of aging, at least in the pathological aging of Alzheimer's disease. Alzheimer's disease is a degenerative disease of the cholinergic central nervous system. In a manner analogous to the treatment of Parkinson's disease by substituting dopamine, progress has been made by substituting acetyl-choline in selected patients with Alzheimer's disease.[21] When it comes to physiological age-related neuronal loss, the cholinergic system may also be the major pathway involved. Here there is an interesting finding of relevance to anaesthesia. Repeated anaesthesia is implicated in accelatating the loss of cholinergic neurons in aging rats.[22]

It is when the role of the cholinergic system is considered outside the narrow confines of anaesthesia that the enormous implications for future research are clear. Fifteen years ago there was a hypothesis that Parkinsonism could be the result of neural toxicity of opioid analogues on dopaminergic neurons.[6] These days it is worth considering chronic postoperative cognitive dysfunction as an aging process triggered by anaesthesia. The consequences are far reaching. For years we have talked of the 'ideal' anaesthetic as one which has no long-term or cumulative effects on the body, and the process of anaesthesia which, properly practised, leaves no traces. It may be that we shall have to modify that view and accept that the brain, at least that of the elderly patient, is not as tolerant of anaesthesia as we previously thought.

Elderly patients present to anaesthetists with very special problems. They are uniquely sensitive to the stresses of trauma, hospitalization and surgery in ways that are only partly understood. Yet at present there is no systematic attempt to train anaesthetists to study these vulnerable patients and care for them more effectively. Anaesthetists concentrate their experience by working with individual surgical specialties in which the concept of age as a normal process is less important than the surgically relevant age-related disease. They do not learn about the elderly in the structured way in which they learn about small children. A generation after a group of far-sighted colleagues persuaded the profession to look at paediatric anaesthesia as 'special'. it is time for the emergence of a new 'subspecialty'. A generation hence and it could be too late. In this issue of the *British Journal of Anaesthesia* we can learn how to start.[3]

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BJA

CLINICAL INVESTIGATIONS

Relationship of the functional recovery after hip arthroplasty to the neuroendocrine and inflammatory responses†

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We studied the relationship between the neuroendocrine and inflammatory responses to hip arthroplasty and functional recovery in 102 patients undergoing elective arthroplasty for osteoarthritis. Blood samples were collected for up to 7 days after surgery and analysed for concentrations of norepinephrine, epinephrine, cortisol, interleukin-6 and C-reactive protein. The primary outcome measures were milestones in hospital, times to walk 10 and 25 m, pain on discharge from hospital, and function 1 and 6 months after surgery. Walking distances in hospital were significantly delayed in patients with greater interleukin 6 and C-reactive protein concentrations, but few neuroendocrine measures had significant correlations with functional recovery in hospital. Multivariate analysis showed that the interleukin 6 concentration on day 1 was the unique predictor of time to walk 10 and 25 m, and that the day 2 concentration of C-reactive protein was the unique predictor of pain on discharge from hospital. No significant correlations were found between the inflammatory and neuroendocrine variables and recovery at 1 and 6 months. We conclude that the inflammatory response affects immediate functional recovery after hip arthroplasty.

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Major surgery causes a variety of physiological, subjective and behavioural changes that are known collectively as the 'stress response' to surgery. Many of these physiological responses have been investigated extensively. In particular, neuroendocrine changes have been reported in the anaesthetic literature[1] relating to the effects of anaesthetic techniques, such as regional anaesthesia and high-dose opioid anaesthesia. Nearly 20 yr ago, Kehlet suggested that the neuroendocrine response to surgery was not essential for survival and could even be detrimental, contributing to postoperative complications and delaying recovery.[2] Despite thorough investigation, the hypothesis that decreasing the neuroendocrine changes will enhance recovery is poorly supported. Indeed, one extensive review of regional anaesthesia and postoperative outcome concluded that more studies were needed to determine the relationship between the stress response and postoperative morbidity.[3]

Endoscopic surgery is associated with improved recovery and more rapid discharge from hospital compared with the equivalent open surgical procedure.[4] Neuroendocrine changes are similar for cholecystectomy by laparoscopy compared with laparotomy, but responses, such as those of interleukin 6 (IL-6) and C-reactive protein (CRP), are decreased.[5] We have suggested that the inflammatory response is more important than neuroendocrine changes in determining recovery.[6] The evidence is particularly

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strong for cholecystectomy but less clear for other surgical operations, such as colectomy. Suitable indices of recovery and surgical outcome are hard to define, and for many procedures functional recovery cannot be measured.

We set out to examine the relationship between the neuroendocrine and inflammatory changes and recovery from primary hip arthroplasty undertaken for osteoarthritis. This operation was chosen because it is a common procedure, causes a major physiological response and allows functional recovery to be assessed.

Methods

Patients

After the local Ethics Committee had given approval (GMB/ARM/93/87), patients admitted for unilateral, primary, elective hip arthroplasty for osteoarthritis were studied. Patients admitted before 17.00 h on the day before surgery and scheduled for surgery before 12.00 h were asked to participate. Exclusion criteria included rheumatoid arthritis, major systemic illness likely to alter neuroendocrine and inflammatory changes, such as diabetes mellitus, and steroid medication within the past 6 months. Of 128 suitable patients, 23 declined to participate. Three patients subsequently withdrew from the study so that 102 patients were included.

Anaesthesia and surgery

Patients were premedicated with an oral benzodiazepine before transfer to the operating theatre. On arrival in the anaesthetic room an i.v. cannula was inserted and a blood sample collected. Anaesthesia was induced with thiopentone (n=88) or propofol (n=14) and, after the administration of a non-depolarizing neuromuscular blocking drug, the trachea was intubated and the lungs ventilated with nitrous oxide, oxygen and isoflurane. Intraoperative analgesia was usually provided with i.v. morphine (2.5–28 mg) and occasionally with i.v. fentanyl (50–250 μg). Standard intraoperative monitoring was undertaken and crystalloid solution used for i.v. fluid replacement. Glucose-containing solutions were not given and packed red cells or whole blood were transfused when necessary. In 88 patients a standardized lateral approach was used for a Charnley hip replacement with a trochanteric osteotomy, and the remaining 14 patients had a Monk procedure with an uncemented femoral prosthesis. Postoperative analgesia was provided first by patient-controlled analgesia with morphine and then with oral analgesics—coproxamol, diclofenac or dihydrocodeine.

Procedure

Written informed consent was obtained. On the day before surgery a blood sample was collected, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was determined [7] and a set of psychological questionnaires was administered (not reported here). The WOMAC index measures arthritis-related disability in the hip joint by patients' responses to questions (scored on a five-point Likert scale) about dysfunction, pain and stiffness during routine activities. Responses to several items are added to give separate scores for functional impairment, pain and stiffness, and these are combined to give a total WOMAC score. Patients were also included in a study of the effects of preoperative psychological preparation on postoperative outcome. In brief, patients were assigned randomly to one of three groups: control, relaxation and imagery. None of the variables described here was altered by the differing psychological management.

Blood samples were collected before induction of anaesthesia (0 h), 1, 2, 4, 8, 12 and 24 h after incision, and then daily for 7 days after surgery. Samples of blood were obtained from a cannula in a forearm vein during the first 24 h and subsequently by direct venepuncture.

Analysis of blood samples

Aliquots of plasma and serum were separated from the blood sample within 30 min of collection and stored at –70°C until analysis. Circulating norepinephrine, epinephrine, cortisol, IL-6 and CRP concentrations were measured by methods described in detail previously.[8] Plasma catecholamines were measured for the first 24 h after surgery only and the remaining variables for 7 days.

Physiotherapy regimen

All patients were seen by a physiotherapist on the day after surgery for chest care and circulatory exercises while on bed rest. After a satisfactory radiograph, all patients were expected to leave the bed with assistance on the second day after surgery. Daily walking practice graduated from frame to crutches or sticks and the distance was increased gradually according to the patient's ability. Before discharge from hospital, all patients were able to walk with aids safely and independently and to climb stairs.

Outcome assessment

The primary outcome measures were milestones in hospital, pain on discharge and function at 1 and 6 months. We have shown recently that the times to walk 10 and 25 m with standardized walking aids are a valid assessment of short-term functional recovery after hip arthroplasty and are sensitive to factors known to alter the rate of recovery, such as the age of the patient and different surgical regimens.[9] The physiotherapist's rating of pain on final mobilization was on the following scale: none, a little, moderate, severe. WOMAC questionnaires were completed at a home visit by one of the research team 1 and 6 months after surgery.

Statistical analysis

To normalize the distribution of the data and homogenize variances, all biochemical data were $\log_{10}$-transformed. For multivariate analyses only, missing data were imputed by a maximum likelihood procedure applied to all measurements of each variable in a single block (SPSS 10.0).

Bivariate analyses were undertaken using product-moment correlations. Multivariate analyses were used to confirm and clarify the findings of the bivariate analysis. The days on which the 10 and 25 m walks were achieved were used to indicate functional recovery and multiple regression was used to examine the prediction of each end-point by the biochemical variables. In multivariate analysis each variable was represented by the value of the peak response. The same procedure was applied to the physiotherapist's final assessment of pain.

Statistical analysis was undertaken with SPSS 10.0 and $P<0.05$ was considered statistically significant.

Results

Details of the 102 patients studied are shown in Table 1. The time course of the biochemical variables is shown in Table 2. A significant correlation was found between the duration of surgery and the peak CRP concentration ($r=0.23$, $P=0.02$) but not with the peak IL-6 concentration ($r=0.19$, $P=0.051$). A detailed description of the endocrine, metabolic and inflammatory responses of 106 patients undergoing primary hip arthroplasty, including the 102 osteoarthritic patients reported here, has been published recently.[8]

There were few postoperative complications: surgical (3), urinary tract infections (3), cardiac (2), respiratory (2), gastrointestinal (2), deep vein thrombosis (1) and other (7).

The mean total WOMAC score decreased from 62 (SEM 1.7) before surgery to 42 (1.6) at 1 month and 27 (2.0) after 6 months. The mean time to walk 10 m was 5 (0.3) days and to walk 25 m was 8 (0.5) days. Mean pain on discharge was 0.28 (0=no pain, 1=little pain).

Prediction of recovery in hospital

No significant correlations were found between preoperative WOMAC and norepinephrine, epinephrine, cortisol and IL-6 concentrations, but a significant correlation was observed with the early CRP response (day −1 to 12 h, $P<0.05$). Walking distances were achieved significantly later in patients with greater IL-6 and CRP concentrations (Fig. 1 and Table 3). This was particularly notable for the CRP results; significant correlations were found for the time to walk both 10 and 25 m from day 3 to day 7 (10 m, $P<0.05$ and $P<0.01$; 25 m, $P<0.05$). Patients with greater CRP concentrations had more severe pain on discharge (8–24 h and days 4 and 5, $P<0.05$; days 2 and 3, $P<0.01$).

There were few statistically significant correlations of functional recovery with the neuroendocrine changes (Table 4) but greater preoperative cortisol concentrations were associated with more rapid recovery and patients with higher norepinephrine concentrations (8, 12 and 24 h) were slower to walk.

Table 1 Details of patients studied. Mean (SD) *Not recorded for one patient; †not recorded for three patients

	Study sample	**Withdrew consent**	**Declined consent**
n	102	3	23
Male:female	37:65	3:0	7·16
Age (yr)	69 (29–87)	73*	69 (28–85)
Duration of surgery (min)	110 (29)		
Intravenous fluids (ml)	2110 (686)		
Blood requirement†			
None	37		
1 unit	22		
≥2 units	40		

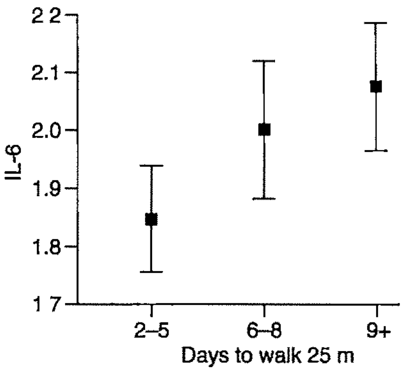

Fig 1 Mean (SEM) $\log_{10}$ IL-6 concentration on day 1 and time to walk 25 m in early (2–5 days), intermediate (6–8 days) and late walkers (≥9 days). Log 1 7 ≈50 pg ml^{-1} and log 2 3 ≈200 pg ml^{-1} IL-6

Multivariate analysis

The pattern of these results was confirmed by multiple linear regression analysis. With time to walk 25 m as the response variable, stepwise entry was used (F-to-enter $P<0.05$, F-to-remove $P<0.10$) for the inflammatory and neuroendocrine variables, each represented by the peak response. One variable contributed uniquely: IL-6 on day 1 [$\beta=0.28$; $b=3.94$, 95% confidence interval (CI) 1.25–6.62]. When time to walk 10 m was used as the response variable in a similar analysis, again only IL-6 on day 1 was significant ($\beta=0.22$; $b=1.78$, 95% CI 0.19–3.36). With pain on discharge as the response variable, one predictor was identified: CRP on day 2 ($\beta=0.31$; $b=0.85$, 95% CI 0.33–1.38).

Recovery at 1 and 6 months

No significant correlations were found between the inflammatory and neuroendocrine variables and the 1 and 6 month WOMAC values.

Table 2 Mean (SEM) circulating concentrations of epinephrine, norepinephrine, cortisol, IL-6 and CRP in patients undergoing hip arthroplasty.

	Day –1	Day 0						Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
		0 h	1 h	2 h	4 h	8 h	12 h							
Epinephrine (pmol litre^{-1})	0.53	0.45	0.69	0.97	1.24	0.89	0.62	0.58						
	(0.04)	(0.03)	(0.10)	(0.12)	(0.16)	(0.09)	(0.06)	(0.08)						
Norepinephrine (pmol litre^{-1})	4.19	3.31	3.79	5.49	6.43	5.41	5.04	4.57						
	(0.21)	(0.19)	(0.29)	(0.33)	(0.47)	(0.44)	(0.39)	(0.26)						
Cortisol (nmol litre^{-1})	375	461	801	816	852	990	875	626	510	562	518	571	564	551
	(15)	(17)	(24)	(23)	(32)	(47)	(44)	(29)	(17)	(23)	(18)	(17)	(15)	(14)
IL-6 (pg ml^{-1})	4.5	5.9	4.9	16.8	72.0	89.2	100.4	129.3	75.8	41.5	27.3	22.0	20.1	18.6
	(0.9)	(1.2)	(0.7)	(1.4)	(4.7)	(8.2)	(9.5)	(14.9)	(8.6)	(6.4)	(5.5)	(2.5)	(2.4)	(2.6)
CRP (mg litre^{-1})	8.0	8.0	7.1	7.9	7.5	10.8	28.4	96.1	157.2	154.1	123.0	98.2	79.0	71.5
	(1.0)	(1.1)	(1.3)	(1.4)	(1.1)	(1.4)	(2.2)	(4.4)	(6.3)	(6.0)	(5.3)	(4.8)	(4.0)	(4.3)

Table 3 Correlations of circulating concentrations of IL-6 and CRP with functional recovery in hospital. Number of days before patient walked 10 and 25 m and physiotherapist's rating of pain on discharge. *P<0.05, †P<0.01

	Walk 10 m	Walk 25 m	Pain
IL-6 (pg ml^{-1})			
Day –1	–0.05	0.11	0.04
Day 0			
2 h	0.03	0.10	0.10
4 h	–0.05	0.05	0.05
8 h	0.17	0.30†	0.17
12 h	0.15	0.32†	0.17
Day 1	0.23*	0.31†	0.27*
Day 2	0.26*	0.25*	0.17
Day 3	0.18	0.18	0.23*
Day 4	0.16	0.23*	0.15
Day 5	0.18	0.21	0.21
Day 6	0.27*	0.27*	0.11
Day 7	0.17	0.24*	0.14
CRP (mg litre^{-1})			
Day –1	–0.06	0.00	0.03
Day 0			
4 h	–0.13	–0.05	0.16
8 h	–0.14	–0.07	0.24*
12 h	–0.05	0.00	0.24*
Day 1	0.09	0.25*	0.27*
Day 2	0.13	0.23*	0.32†
Day 3	0.25*	0.27*	0.34†
Day 4	0.24*	0.26*	0.27*
Day 5	0.33†	0.28*	0.23*
Day 6	0.29†	0.27*	0.08
Day 7	0.29†	0.25*	0.17

Table 4 Significant correlations of circulating concentrations of norepinephrine, epinephrine and cortisol with functional recovery in hospital. Number of days before patient walked 10 and 25 m and physiotherapist's rating of pain on discharge. Correlations not shown were not significant. *P<0.05

	Walk 10 m	Walk 25 m	Pain
Norepinephrine (pmol litre^{-1})			
Day 0, 8 h	0.24*	0.25*	–0.08
Day 0, 12 h	0.17	0.22*	–0.01
Day 0, 24 h	0.10	0.25*	–0.10
Epinephrine (pmol litre^{-1})			
Day 0, 4 h	–0.23*	–0.11	0.00
Cortisol (nmol litre^{-1})			
Day –1	–0.25*	–0.24*	–0.27*
Day 0, 4 h	–0.21*	–0.08	–0.20
Day 2	0.03	0.23*	0.11

Discussion

We found that the inflammatory response to hip arthroplasty, measured as circulating IL-6 and CRP concentrations, was related to functional recovery. In contrast, the classical neuroendocrine changes—norepinephrine, epinephrine and cortisol concentrations—were relatively unimportant. Furthermore, no relationship was found between the circulating variables measured for up to 7 days after surgery and outcome at 1 and 6 months.

Although the significant correlation coefficients for the inflammatory markers and functional recovery were not high, those for CRP in particular were consistent over several days (Table 3). Subsequent multivariate analysis confirmed the importance of the inflammatory response, as the peak IL-6 value was the unique predictor of time to walk 10 and 25 m and peak CRP predicted pain on discharge. Although perioperative factors, such as haemodilution, red cell transfusion and differing doses of opioids, could affect circulating hormonal and inflammatory variables, small changes in clinical management would have weakened the relationship of the measured variables with recovery. In this descriptive study we chose to reflect clinical practice and did not attempt to control perioperative management. The strengths of the investigation were the large number of patients investigated, the use of one operation for a single pathology, the prolonged sampling schedule and the measurement of functional recovery.

The lack of influence of circulating cortisol, norepinephrine and epinephrine on indices of recovery was in marked contrast to the inflammatory variables (Table 4). The significant negative correlations of cortisol concentrations on the day before surgery with times to walk 10 and 25 m and pain on discharge, were unexpected. It suggests that greater cortisol secretion improves recovery. The mechanism could perhaps be increased anti-inflammatory activity and the mood-enhancing effects of glucocorticoids.[10] It is notable that this inverse relationship was not found for increased cortisol secretion after surgery except for an isolated significant correlation at 4 h. The influence of preoperative factors was also shown by the correlations between preoperative WOMAC scores and CRP concentrations for the first 12 h after surgery. It is probable that the severity of the osteoarthritis affected the early CRP response before the inflammatory changes induced by surgery became dominant after 12 h. An association between norepinephrine concentrations at 8, 12 and 24 h and times to walk 10 and 25 m was not found for epinephrine. The clinical relevance of these observations is unknown, but it is possible that suppression of adrenergic responses after surgery may confer benefits other than on the myocardium and vasculature.

These results support the hypothesis, deduced from a comparison of cholecystectomy by laparoscopy versus laparotomy, that the inflammatory response is the primary determinant of recovery.[6] Furthermore, this hypothesis can explain why regional anaesthesia, in spite of excellent analgesia, has consistently failed to enhance recovery.[3 11] Although regional anaesthesia may attenuate, and occasionally even abolish, the neuroendocrine response to surgery, the inflammatory changes are not affected.[12 13] The inability of regional anaesthesia to modify the cytokine response to surgery confirms a seminal study in 1980 that found that extensive epidural blockade did not attenuate the acute-phase response to surgery.[14]

At present there are no anaesthetic techniques that have been shown to decrease the inflammatory response consistently. Large doses of the opioid alfentanil, when used as part of a total i.v. technique, suppressed IL-6 secretion transiently.[15] Further studies with low- and high-dose fentanyl failed to confirm these findings.[16 17] Glucocorticoids suppress IL-6 production by an action on cytokine gene expression[18] and a clinical effect has been demonstrated with large doses given before surgery.[19] Unfortunately, the dose needed (methylprednisolone 30 mg kg^{-1}) caused deleterious side-effects (failure of intestinal anastomosis and wound dehiscence) although a later study claimed that no major problems occurred.[20] The important reciprocal interaction between IL-6 and glucocorticoids was shown in a study using etomidate, in which IL-6 release was increased transiently by inhibition of adrenal steroidogenesis.[21]

Non-steroidal anti-inflammatory drugs (NSAIDs) could decrease the inflammatory response to surgery and are widely used. The results are conflicting, although this may reflect the surgical models used and the dose regimens of the NSAIDs.[22–24] A new class of drugs for use in rheumatoid arthritis that not only acts as an NSAID but also inhibits cytokine synthesis offers the possibility of testing the hypothesis directly.[25] At present, decreasing surgical trauma, either by laparoscopy or the use of a smaller incision, is the only way to reduce the inflammatory response.

In conclusion, the notion that the neuroendocrine response to surgery influences recovery is not tenable for primary hip arthroplasty. Instead, attention should be focused on the inflammatory changes that we have shown to be implicated in functional recovery.

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Development and testing of a hierarchical method to code the reason for admission to intensive care units: the ICNARC Coding Method

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A computer-based hierarchical method was developed to code conditions leading to admission to intensive care in the UK. The hierarchy had five tiers: surgical status, body system, anatomical site, physiological or pathological process and medical condition. The hierarchy was populated initially using the free-text descriptions of the reason for admission from 10 806 admissions recorded as part of the Intensive Care Society's UK APACHE II study. After refinement and error-checking, a prospective evaluation was undertaken on 22 059 admissions to 62 UK intensive care units. Individual units coded between 60 and 1610 (mean 356) admissions. All but 50 (0.2%) of the admissions could be coded and 38 units coded every admission. Fifty admissions (0.2%) could not be coded within 24 h of admission but were coded subsequently when more information became available. Of the admissions, 96.1% were coded at all levels of the hierarchy in the coding method. Six hundred and thirty-seven of the 741 unique conditions (85.9%) were used in one of the five reasons for admission and 564 (76.1%) in the primary reason for admission. Five conditions account for 19.4% of all primary reasons for admission. This is the first method to be developed empirically for coding the reason for intensive care admission.

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A systematic method for recording the reason for admission to intensive care is central to the analysis, interpretation and comparison of mortality and morbidity data collected in different units, countries or at different times. The conditions have to be coded to ensure consistent terminology and to allow statistical analysis and modelling. The Intensive Care Society's UK APACHE II study[1–3] used a modified version of the American APACHE II 'primary indication for ICU admission' classification method to code the reason for admission to intensive care into multiple categories. In spite of the modifications, which removed impossible combinations of the seven body systems and 36 precipitating factors from the American APACHE II classification (e.g. the combination of body system, gastrointestinal with precipitating factor, and valvular heart disease), problems were still encountered by study participants trying to code the reason for admission.

Many of the problems arose because the categories ranged from discrete, well-defined conditions (e.g. diabetic ketoacidosis) to groups of conditions (e.g. peripheral vascular surgery) and were neither comprehensive nor exclusive. In addition, it was often difficult to identify a single primary reason for admission and there was no provision for coding other important conditions occurring either during or after the first 24 h. If the American APACHE II rules were followed strictly (only information available during the first 24 h to be used to code the reason for admission), there was no provision to update the reason for admission if it could be provided, either in more detail or more appropriately, after the first 24 h.

Moreover, the categories could not be cross-mapped to either of the two main diagnostic coding methods in use in the UK, the Read codes [4] and the International

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Classification of Diseases (ICD-9/10). The lack of precision in the categories also impaired the ability to compare the mortality rates for single conditions with published case series.

As part of its remit to establish a national comparative audit of patient outcome from intensive care, the Intensive Care National Audit & Research Centre (ICNARC) convened a working group to develop and test an improved method for coding the reason for admission to adult and paediatric intensive care and high-dependency units. The primary requirement for the method was that it would add explanatory power when attempting to estimate the probability of hospital death after intensive and high-dependency care. Other requirements included the ability to describe the workload of an intensive care unit (ICU) in order to be able to compare it with other units' workloads and to relate a unit's activity to the workload of the hospital. The coding method would have to be able to code multiple reasons for admission in sufficient detail to be of value to clinicians and be capable of cross-mapping to other coding methods. As the coding method was to be used in conjunction with physiological data, it had to describe the underlying cause of deranged physiology (e.g. splenic trauma) rather than simply duplicating physiological information by describing the pattern of physiological changes (e.g. hypovolaemic shock).

This paper describes the development, testing and final form of the coding method, now called the ICNARC Coding Method (ICM).

Methods

Literature review

A literature search was undertaken to locate any published intensive care-specific coding methods that predated or postdated the APACHE II method. As none were found, direct approaches were made to groups known to be active in the field to identify any unpublished methods. The following unpublished methods were identified: the Fichier Diagnostique (January 1994 update), the classification method of the Société de Réanimation de Langue Français; a list of conditions produced collaboratively by the developers of the Mortality Probability Models (MPM II) and the Simplified Acute Physiology Score (SAPS II); a list of conditions forming the interim results of the Diagnosis Task Force from Project IMPACT in the USA; two other lists of conditions based on ICD-9 and Diagnostic-Related Groups; and the diagnostic coding methods used in the development and final implementation of the APACHE III method. From the systematic search of the published and unpublished literature, it was apparent that none of the existing methods for coding the reason for admission to intensive care had been derived empirically.

Outside intensive care, other generic diagnostic and procedural coding methods were available. The three in most common use in the UK were the ICD-9 or 10, the Read codes (or CTV3), developed by Dr James Read for computerized records in general practice, and the Office of Population and Censuses and Surveys procedural coding system (OPCS4). These were all exhaustively comprehensive, but this was also their disadvantage in that they contained large numbers of conditions that were irrelevant to both intensive care and high-dependency care and would, therefore, be very cumbersome to use.

Development of a coding method

A free-text description of the reason for admission had been collected for each of 10 806 admissions to the 26 ICUs that participated in the UK APACHE II study. In most cases, this free-text description was augmented with an APACHE II diagnostic code. This provided a core data set from which the coding method was developed.

Before analysis of the qualitative data, a theoretical structure for the coding method was proposed, based on the available published and unpublished methods, and consensus within the working group of seven senior intensive care physicians and researchers. A computer-based, hierarchical structure, coding by body system, then by anatomical site, then by physiological or pathological process ('system: site:process' structure) was proposed. A prototype hierarchy was prepared for the respiratory system, and this structure was then applied by the clinical members of the group to all patients with a respiratory condition in the data set (non-surgical, n=1556; surgical, n=1374). Although the hierarchical system worked well, a three-tiered hierarchy was insufficiently detailed to code comprehensively the respiratory conditions in the data set. A four-tiered hierarchical system with the structure 'system:site:process:condition' was piloted on a subgroup of the respiratory system group (APACHE II diagnostic group 'respiratory system: aspiration/poisoning/toxic', n=149), which provided the required level of detail.

A full four-tiered coding method was then derived for all body systems, using the diagnostic information from the data set. After ensuring consistency of terminology between body systems, the method was checked to ensure that all the reasons for admission found in the five unpublished coding lists were included, and checks were made with standard textbooks to ensure that no common conditions had been missed. A fifth tier was added to code whether the reason for admission was a condition for which the patient had had surgery. This gave a final five-tier structure of 'type: system:site:process:condition'. This was then cross-mapped to both the UK and the US APACHE II classification methods where possible (not all reasons for admission have an APACHE II code, e.g. burns).

Testing the coding method

The resulting coding method was tested initially against the data used to derive it. All 10 806 conditions in the data set were coded using the new method to ensure that there were no omissions or inconsistencies. The coding method was then tested retrospectively by coding 140 recorded reasons for admission from one general ICU, and then prospectively in three ICUs where members of the working group practised. Finally, the method was tested in five independent ICUs. At each stage the method was modified to remove inconsistencies and include any omitted reasons for admission.

The coding method was then used by all ICUs contributing data to the national audit of intensive and high-dependency care (the Case Mix Programme). Two members of staff from each unit received a half-day's training in the background and use of the coding method, a detailed manual and ongoing support from ICNARC. To date, the method has been used for over 3 yr to code the reason for admission for 62 780 patients. User feedback has resulted in four minor revisions to date.

Results

Description of the ICNARC Coding Method

The final hierarchy has five tiers: type, system, site, process and condition.

- Type: is it a surgical code (reason for surgery) or non-surgical code?
- System: which body system is involved?
- Site: which anatomical site is involved?
- Process: which physiological or pathological process is involved?
- Condition: what is the name of the condition?

Figure 1 shows how the ICM would be used to code a patient with pneumococcal pneumonia.

The 12 possible body systems and 55 pathological or physiological processes are shown in Table 1. There are three systems that do not correspond to conventional anatomical or physiological body systems. The psychiatric system is used to code for mental health conditions and has no anatomical site tier. The trauma and poisoning systems are simply for user convenience when coding multiple trauma or poisoning and are duplicates of all the conditions in which the process tier is either trauma or poisoning, thus reordering the hierarchy into 'type:process:system:site:condition'.

The ICM was developed to code up to five reasons for admission. These are the primary reason for admission to intensive care (corresponding to the APACHE II primary indication for ICU admission); the secondary reason for admission to intensive care; up to two other conditions relevant to the admission; and a field allowing revision of the primary reason if further information became available after the first 24 h. As a result, the ICM has to allow coding of conditions that would never be a primary reason for admission to intensive care, but might be a secondary reason. A simple example would be a patient admitted after a suicide attempt with a paracetamol overdose. The reason for admission is clearly self-poisoning with paracetamol. However, if the patient took the overdose as a result of depression and the clinician felt this was a relevant condition, this could be coded with the psychiatric system.

The ICM also contains a number of minor surgical conditions, such as inguinal hernia. These are included to allow coding of the surgical condition when patients are admitted for a complication of surgery or anaesthesia, such as persistent neuromuscular blockade as a result of pseudocholinesterase deficiency.

Specific comorbidity (chronic health history) required for the APACHE II method and the MPM IIs is recorded separately, as there are very specific requirements for both diagnostic detail and timing.

The ICM was developed to be as user-friendly as possible. As a result, conditions that affect more than one body system are coded under all the relevant systems. This occurs most commonly with neurological conditions affecting the respiratory system; for example, a patient with Guillain–Barré syndrome can be coded by two routes:

- Type: non-surgical code
- System: neurological
- Site: peripheral nervous system
- Process: inflammation
- Condition: Guillain–Barré syndrome

or

- Type: non-surgical code
- System: respiratory
- Site: peripheral nervous system disorders causing respiratory failure
- Process: inflammation
- Condition: Guillain–Barré syndrome.

This duplication of final codes means there are 1140 final codes but only 741 unique conditions. The codes corresponding to each unique condition are linked to find the overall incidence of the condition.

If a user has no clear idea of the condition that precipitated admission to intensive care, or if the condition that the patient is suffering from does not appear in the coding method, the coding can be limited to 'type:system:site' or 'type:system:site:process'. If an admission cannot be coded to full depth, the user is encouraged to give the reason for admission as a text description, both to allow recognition and eventual incorporation of very rare conditions and to allow the ICM to be updated with missing, more common, conditions. The ICM was designed to be used in conjunction with a physiological data set, so non-specific syndromes, which are defined by a range of physiological abnormalities (e.g. the systemic inflammatory response syndrome), are not included as they should be determined objectively from physiological data.

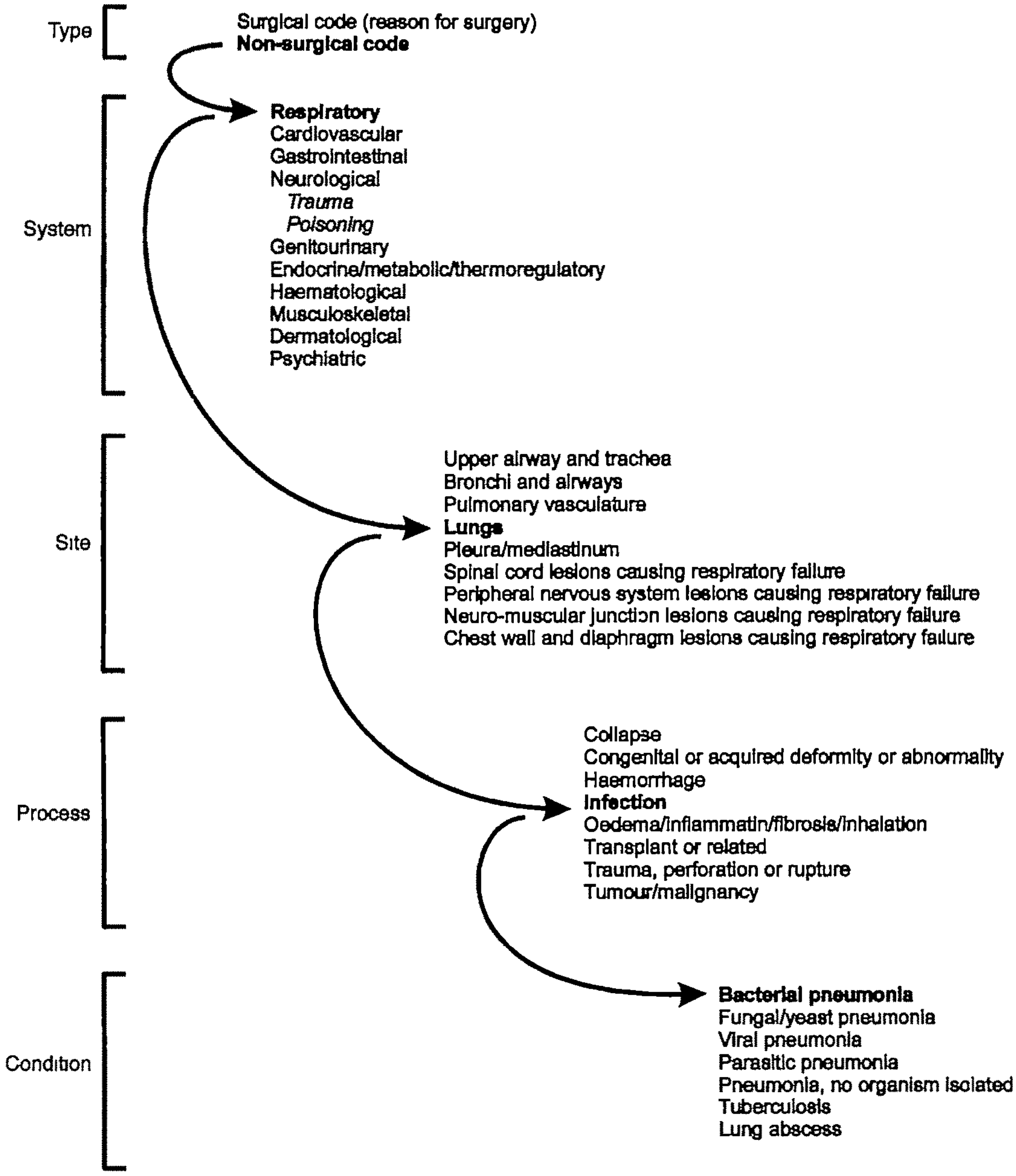
Type
Surgical code (reason for surgery)
Non-surgical code
System
Respiratory
Cardiovascular
Gastrointestinal
Neurological
Trauma
Poisoning
Genitourinary
Endocrine/metabolic/thermoregulatory
Haematological
Musculoskeletal
Dermatological
Psychiatric
Site
Upper airway and trachea
Bronchi and airways
Pulmonary vasculature
Lungs
Pleura/mediastinum
Spinal cord lesions causing respiratory failure
Peripheral nervous system lesions causing respiratory failure
Neuro-muscular junction lesions causing respiratory failure
Chest wall and diaphragm lesions causing respiratory failure
Process
Collapse
Congenital or acquired deformity or abnormality
Haemorrhage
Infection
Oedema/inflammatin/fibrosis/inhalation
Transplant or related
Trauma, perforation or rupture
Tumour/malignancy
Condition
Bacterial pneumonia
Fungal/yeast pneumonia
Viral pneumonia
Parasitic pneumonia
Pneumonia, no organism isolated
Tuberculosis
Lung abscess

Fig 1 An example of how the coding method would be used to code a patient with bacterial pneumonia. The patient did not have surgery for the condition, so the first tier is non-surgical. The body system involved is the respiratory system, and the anatomical site is the lungs. The process is infection and the condition is bacterial pneumonia The computer generates a numerical code that describes the route through the hierarchy.

Numerical results

The ICM has been used on 62 780 admissions to 118 ICUs, from which data on 22 059 admissions to 62 ICUs UK have been validated to date. Results are only given for validated data. Individual ICUs have coded between 60 and 1610 (mean 356) admissions. All but 50 (0.2%) of the admissions could be coded, 38 of the ICUs were able to code every admission and the maximum number of uncoded admissions for any unit was 7 (2.9%). Fifty (0.2%) admissions could not be coded in the first 24 h of admission but were subsequently coded when more information became available after that period. Of the admissions, 96.1% were fully coded to the full level of detail in the coding method (type:system:site:process:condition) in the primary reason for admission.

The fields required to code the admissions (from the primary reason for admission to intensive care, the secondary reason for admission to intensive care, two other conditions relevant to the admission) are shown in Table 2. Six hundred and thirty-seven of the total of 741 unique conditions (85.9%) have been used in one of the fields in the

Table 1 The body systems and all the processes used in the ICM The body system is qualified by the anatomical site and the process by the condition. The order of the systems in the system tier of the hierarchy was determined by the frequency of admissions in the UK APACHE II study; the most common system is at the top. Only a subset of relevant processes is presented for each anatomical site, as can be seen in Fig. 1

Body systems	Processes
Respiratory	Accidental intoxication or poisoning
Cardiovascular	Acidaemia
Gastrointestinal	Affective disorder
Neurological	Alcohol and drug dependence
Trauma	Alcohol-related disorders
Poisoning	Alkalaemia
Genitourinary	Burns/hyperthermia
Endocrine/metabolic/ thermoregulatory	Chromosomal deletion syndromes
	Collapse
Haematological	Coma or encephalopathy
Musculoskeletal	Congenital or acquired deformity or abnormality
Dermatological	Contiguous gene syndromes
Psychiatric	Degeneration
	Diabetes mellitus
	Dissection or aneurysm
	Envenomation
	Epidural/spinal drug administration
	Failure
	Fluid overload
	Haemolysis/thrombocytopenia
	Haemorrhage
	Hypercalcaemia
	Hyperglycaemia
	Hyperkalaemia
	Hypernatraemia
	Hypertension
	Hyperthermia
	Hypocalcaemia
	Hypoglycaemia
	Hypokalaemia
	Hyponatraemia
	Hypoplasia/dysplasia
	Hypothermia
	Inborn errors of metabolism
	Infection
	Inflammation
	Mental handicap
	Neurosis or personality disorder
	Obesity
	Obstruction
	Obstruction or embolus
	Oedema/inflammation/fibrosis and inhalation
	Overactivity
	Schizophrenia
	Seizures
	Self-intoxication or self-poisoning
	Sex chromosome disorders
	Shock and hypotension
	Starvation
	Transplant or related
	Trauma
	Trisomy
	Tumour/malignancy
	Underactivity
	Vascular

22 059 admissions, 564 (76.1%) in the primary reason for admission. Five conditions account for 19.4% of all the primary reasons for admission. These are: aortic (abdominal) or iliac dissection or aneurysm (*n*=1444, 6.5%), acute myocardial infarction (*n*=878, 4.0%), pneumonia with no organism isolated (*n*=678, 3.1%), bacterial pneumonia (*n*=657, 3.0%) and primary brain injury (*n*=616, 2.8%).

Discussion

This is first time a method for coding the reason for admission to intensive care has been developed empirically from good qualitative data. All other intensive care-specific methods have been based on expert opinion. The use of a large database of text descriptions of reasons for admission to develop and test the method ensured that all common conditions were included; this was confirmed by the very low rate (0.2%) of admissions that could not be coded and the high rate (96.1%) of fully coded admissions in the prospective evaluation. An average-sized ICU in the UK has about 500 admissions a year, so 22 059 admissions represents the equivalent of over 40 yr of admissions, a physician's working life. Thus, any conditions not included will represent no more than a tiny fraction of any ICU's workload.

Many of the intensive care-specific coding methods include some element of hierarchical coding. The APACHE II method divides admissions by surgical status as the first tier, then by body system as the second, and then by one of 36 precipitating factors as the third tier. The APACHE III method divides admissions by body system as the first tier and surgical status as the second, with a list of conditions as the third tier. The Fichier Diagnostique divides admissions by body system as the first tier, at the second tier by 'symptoms, syndromes and failures'/'illnesses and diseases'/'chronic illnesses', and by a mixture of anatomical sites and processes as the third and final tier. The computerized hierarchical structure developed for the ICM is far more detailed and consistent than previous methods. Unlike the APACHE II system, the ICM presents only relevant choices at each level (Fig. 1), so rapid selection of a single condition from over 700 possible options is possible. Results of independent inter-rater reliability testing[5] suggest that the inter-physician agreement is good (κ=0.7 for condition, 0.66 for process, 0.72 for site and 0.77 for system). Given the multiple routes to final conditions, κ values will always underestimate the level of inter-observer agreement, so the agreement is probably far better than these figures suggest. Further testing is warranted.

By collecting data on reasons for admission down to the condition level using a standard, detailed, hierarchical method, the number of potential uses is increased. Any one of the 741 unique conditions, however common or rare, can be studied. In addition, data can be pooled at any level of the hierarchy, for example gastrointestinal conditions (body system), gastrointestinal tumours (body system/process) and gastric tumours (body system/site/process). Data can be pooled both from a clinical perspective (conditions that are similar clinically) or from a statistical perspective (conditions that exhibit similar characteristics, such as similar outcomes). By supplementing the reason for admission data

Table 2 The distribution of the fields used to code the reason for admission for 22 059 admissions

	Primary reason alone used	**Primary and secondary reason used**	**Primary, secondary and one other reason used**	**Primary, secondary and both other reasons used**
Overall percentage	44.4%	25.7%	21 1%	6.0%
Cumulative percentage	44.4%	70.1%	91.2%	97.1%
Individual units range	0–87 7%	0–60.2%	0 2–65.2%	0–26.9%

with the sociodemographic, physiological and outcome data, important descriptive information can be obtained. These additional data allow further options for grouping, for example, grouping by sex or severity of illness for the same condition. The reason for admission can be pooled at various levels to provide sufficient sample sizes to employ statistical models to explain and predict outcome. The ICM combines a high level of detail about individual reasons for admission with a standardized, repeatable method to coalesce rare reasons for admission into groups of sufficient size for statistical analysis.

All ICUs participating in the national comparative audit of patient outcome (Case Mix Programme) have to supply at least one coded reason for admission for each patient. In addition, ICUs are asked to code any other conditions they feel are relevant to the admission, but this is not mandatory. The use of other fields is widely variable across ICUs, suggesting that opinions regarding the relevance of other conditions vary. Clearly, techniques to improve the consistency of coding for secondary and other conditions must be explored and developed.

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Anaphylaxis during anaesthesia. Results of a two-year survey in France

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Between January 1, 1997 and December 31, 1998, 467 patients were referred to one of the allergo-anaesthesia centres of the French GERAP (Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques) network and were diagnosed as having anaphylaxis during anaesthesia. Diagnosis was established on the basis of clinical history, skin tests and/or a specific IgE assay. The most frequent cause of anaphylaxis was a neuromuscular blocking agent (69.2%). Latex was less frequently incriminated (12.1%) than in previous reports. A significant difference was observed between the incidence of anaphylactic reactions observed with each neuromuscular blocking agent and the number of patients who received each drug during anaesthesia in France throughout the study period ($P<0.0001$). Succinylcholine and rocuronium were most frequently incriminated. Clinical reactions to neuromuscular blocking drugs were more severe than to latex. The diagnostic value of specific IgE assays was confirmed. These results are consistent with changes in the epidemiology of anaphylaxis related to anaesthesia and are an incentive for the further development of allergo-anaesthesia clinical networks.

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Anaphylactic reactions to anaesthetic and associated agents used during the perioperative period have been reported with increasing frequency in most developed countries. The estimated incidence of anaphylaxis was between 1 in 10 000 and 1 in 20 000 in Australia in 1993,[1] and was 1 in 13 000 in France in 1996.[2] Although rare,[2] these reactions may lead to death, even when appropriately treated.[2 3] Most published reports concerning the incidence of anaphylaxis originate in France,[2 4] Australia,[5 6] the UK[7 8] and New Zealand.[9] These reflect a long-term policy of systematic clinical and/or biological investigation of anaphylactoid reactions that are thought to be mediated by an immune mechanism.

The number of anaesthetic drugs is increasing, and active pharmacological surveillance of rare unexpected adverse effects of therapeutic agents is now regarded as essential.[10] In addition, guidelines for the identification and/or management of high-risk groups have been proposed.[11 12] Consequently, the confirmation and quantitative risk assessment of suspected rare serious adverse reactions require proper epidemiological studies.

Clinical symptoms and reaction severity do not allow one to distinguish between an immune-mediated anaphylactic reaction and an anaphylactoid reaction resulting from direct non-specific histamine release.[2 13] Furthermore, no specific treatment has been shown to prevent the occurrence of anaphylactic reactions reliably.[13] As a result, the only rational approach to a patient with perioperative symptoms consistent with either an anaphylactoid or an anaphylactic reaction is to assess precisely the type of reaction, to note the drugs responsible and eventual cross-reactivity with related drugs, and to avoid subsequent administration of incriminated drugs or agents. Diagnosis of type I allergy, mediated by specific IgE antibody, is usually confirmed by skin tests,[9 14 15] supported whenever possible by specific IgE assays.[16]

In this paper we report the results of a 2-yr survey of the incidence of anaphylaxis during anaesthesia (1997–1998) conducted by the GERAP (Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques), a network of 38 French allergo-anaesthesia outpatient clinics.

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Patients and methods

This was a retrospective study involving patients who had experienced an adverse anaphylactic reaction during anaesthesia between January 1, 1997 and December 31, 1998. In each case the immune mechanism of the reaction was confirmed on the basis of a standardized diagnostic protocol performed in an allergo-anaesthesia outpatient clinic. All the centres were members of the GERAP network, which was set up in 1985.

The protocol included a questionnaire about age at the time of reaction, sex, number of previous anaesthetic procedures, history of allergy (possible history of atopy, drug, food or latex intolerance), date of the reaction, and drugs used before the reaction. Details were obtained about the degree of reaction, which was graded from I to IV depending on increasing severity [grade I = presence of cutaneous signs; grade II = presence of measurable but not life-threatening symptoms, including cutaneous effects, arterial hypotension (defined as a decrease of more than 30% in arterial blood pressure associated with unexplained tachycardia), cough or difficulty in mechanical ventilation; grade III = presence of life-threatening reactions: cardiovascular collapse, tachycardia or bradycardia, arrhythmias, severe bronchospasm; grade IV = circulatory inefficacy, cardiac and/or respiratory arrest].

Information about allergy investigations was recorded systematically: date of incident, type of skin tests performed (skin prick-test and/or intradermal testing), dilution of the tested drug leading to a positive reaction, cross-reactivity in cases of adverse reaction to a neuromuscular blocking agent, results of histamine and tryptase monitoring during the adverse reaction, and of IgE-specific assays testing responses to quaternary ammonium or latex when available.

Skin tests were performed according to standardized procedures recommended by the Commission Tripartite en Allergologie.[17] Prick and intradermal tests were accompanied by control tests carried out with negative (0.4% phenol in saline) and positive (9% codeine phosphate) controls to determine whether the skin was liable to release histamine and react to it.

Prick tests were performed on the anterior part of the forearm using a drop of undiluted drug in the cases of opioids, hypnotics, colloids and neuromuscular blocking agents, with the exception of atracurium, mivacurium and morphine, which were tested with a 1/10 dilution of the commercially available drug. Prick tests with latex were performed using a standardized commercial fresh natural rubber latex extract (Stallergenes, France). Skin tests were interpreted after 15 min. A prick test was considered positive when the diameter of the wheal was at least half of that produced by the codeine test and at least 3 mm greater than the negative control.

Intradermal tests with neuromuscular blocking agents were carried out after the results of prick tests had been obtained. However, in 12 centres, these were not performed when prick test results were strongly positive. Intradermal tests were performed by injection of 0.02–0.05 ml of drugs diluted in 0.4% phenol physiological solution. Injections were performed every 15 min, according to a dilution scale, beginning with a 10^{-4} dilution when the prick test was positive and a 10^{-3} dilution when the prick test was negative. Injection dilutions were increased progressively to 10^{-1} for aminosteroid neuromuscular blocking agents, as long as the results remained negative. For atracurium and mivacurium, a maximal dilution of 10^{-3} was used when tests were performed on the forearm and 10^{-2} when performed on the back. Intradermal tests were considered positive when the diameter of the wheal was at least 8 mm, with a surrounding flare. When the test was positive, cross-reactivity to other neuromuscular blocking agents was investigated.

The presence of specific IgE against muscle relaxants was investigated using radioimmunoassay (RIA) based on coupling of a choline analogue to Sepharose (QAS RIA, positive threshold 1.5%) or *p*-aminophenylphosphorylcholine to agarose (PAPPC RIA, positive threshold 1%), as described elsewhere.[18 19] The specificity of antibodies against the suspected neuromuscular blocking agent was confirmed by an inhibition step performed with the drug (inhibition required >15%).

In vitro testing for latex-specific IgE was carried out using RAST (Cap System; Pharmacia, France) according to the manufacturer's instructions. Values of allergen-specific IgE above 0.35 kU l^{-1} were considered positive. Plasma concentrations of histamine (RIA Histamine; Immunotech) and tryptase (UniCAP Tryptase, Pharmacia & Upjohn, France) were determined with commercially available RIA kits. Values above 9 nmol l^{-1} for histamine and 12 μg l^{-1} for tryptase were considered to be positive.

Anaphylaxis was diagnosed on the basis of skin test and/or IgE assay results consistent with the clinical history of the adverse reaction and the anaesthetic protocol. To reduce further the risk of false positives when intradermal skin test positivity for aminosteroid neuromuscular blocking agents was observed only at 1/10 dilution, the presence of specific IgE on RIA assay was required to confirm sensitization to the neuromuscular blocking agent administered at the time of the reaction.

To compare the incidences of anaphylaxis to available neuromuscular blocking agents, the number of vials of each agent sold in France in 1997 and 1998 was obtained from the pharmaceutical companies that marketed these drugs (Glaxo Wellcome, Organon Teknika, Pharmacia & Upjohn, Rhône Poulenc Rorer). The number of vials effectively used in anaesthesia was then estimated on the basis of data obtained from a market survey in France, which provided an estimate of the consumption of each neuromuscular blocking agent and its respective use during anaesthesia in intensive care units and in emergency settings in a representative sample of 100 French hospitals (data obtained from *Le Panel Hospitalier*, MAPI, Lyon, Edition

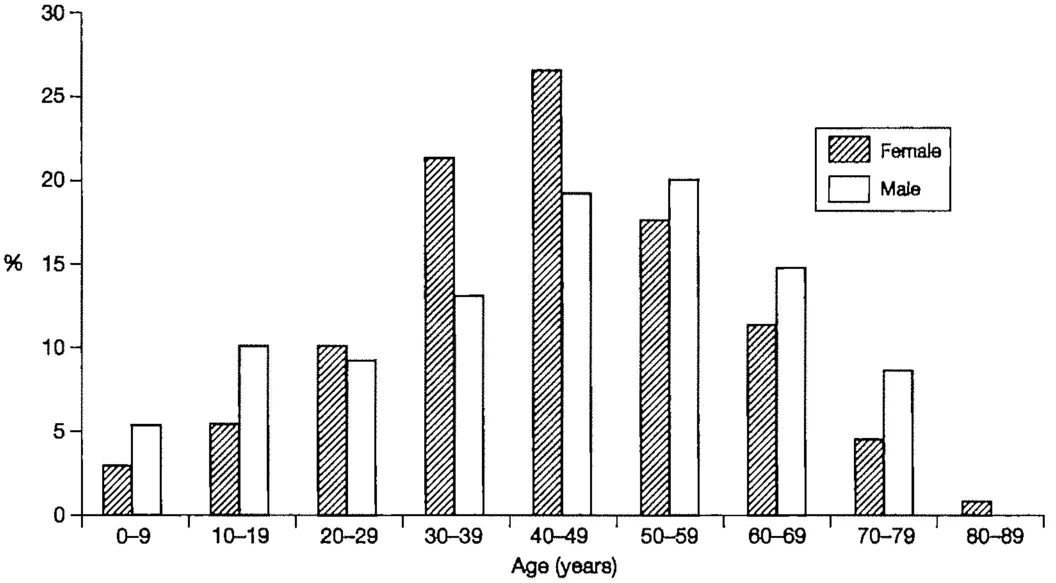

Fig 1 Distribution of anaphylactic reactions in France between January 1997 and December 1998 according to sex and age range (males n=130, females n=342).

Domaine Medical, 1998). To estimate the number of patients effectively exposed to each compound, a correction factor was applied. This factor took the average number of vials of a specific neuromuscular blocking agent used during a standard anaesthetic procedure into account. It depended on the commercially available presentation of the neuromuscular blocking agent, and was established in accordance with Glaxo Wellcome and Organon Teknika for the products they sold.

Statistical analysis

StatView IV software (Abacus Concepts, Berkeley, CA, USA) was used. Results are expressed as mean (SEM). Comparisons were performed using the χ^2 test or analysis of variance when appropriate. $P \leq 0.05$ was considered statistically significant.

Results

Subjects

Four hundred and seventy-seven patients who presented with an anaphylactic reaction during the study period were registered. A significant female predominance was observed [female, n=347 (72.7%); male, n=130 (27.3), $P<0.0001$] in comparison with the percentage of anaesthetic procedures performed in men and women determined in the 1996 survey of anaesthesia in France (female, 55%; male, 45%).[20] This predominance was observed irrespective of the causal agent. The age distribution was as follows: 1–10 yr, n=17 (3.56%); 10–20 yr, n=32 (6.71%); 20–30 yr, n=47 (9.85%); 30–40 yr, n=91 (19.08%); 40–50 yr, n=117 (24.53%); 50–60 yr, n=87 (18.24%); 60–70 yr, n=58 (12.16%); 70–80 yr, n=26 (5.45%); 80–90 yr, n=2 (0.42%). The distribution according to age and sex is shown in Fig. 1. Peak incidence was in the fourth decade in the female group and in the fifth decade in the male group.

Causal agents

The most common cause of adverse reactions was neuromuscular blocking drugs (n=336, 69.2%), followed by latex (n=59, 12.1%) and antibiotics (n=39, 8%) (Table 1). Hypnotics and opioids were involved in 18 (3.7%) and seven (1.4%) cases respectively, colloids in 13 cases (2.7%) and other substances in 14 cases (2.9%; propacetamol, n=4; aprotinin, n=2; chymopapain, n=2; protamine, n=1; bupivacaine, n=1; ketoprofen, n=1; hyaluronidase, n=1; methylene blue, n=1; ethylene oxide, n=1).

In nine cases, patients were found to be sensitized to two different agents: a neuromuscular blocking agent and latex in three cases, a neuromuscular blocking agent and propofol in two cases, a neuromuscular blocking agent and methylene blue in one case, latex and a colloid in one case, latex and ethylene oxide in one case, and propofol and a colloid in one case.

History of atopy, allergy, asthma or a previous adverse reaction during anaesthesia

Atopy was present in 121 cases (25.4%), and asthma in 41 cases (8.6%). A history of drug intolerance was reported in 76 cases (15.9%) and food allergy was present in 14 cases (2.9%). When latex and neuromuscular blocking agents were compared, atopy appeared to be significantly more frequent in the case of latex allergy (39 *vs* 24.8%, $P<0.01$).

Table 1 Agents involved in anaphylactic reactions during anaesthesia in France between January 1997 and December 1998

Causal agent	Number of patients
Neuromuscular blocking agents (*n*=336, 69.2%)	
Succinylcholine	78
Vecuronium	59
Rocuronium	98
Pancuronium	20
Atracurium	71
Cisatracurium	1
Mivacurium	9
Latex (*n*=59, 12.1%)	59
Antibiotics (*n*=39, 8.0%)	
Penicillin	22
Cephalosporin	11
Vancomycin	2
Rifamycin	1
Quinolone	3
Hypnotics (*n*=18, 3.7%)	
Thiopental	5
Propofol	10
Midazolam	3
Opioids (*n*=7, 1.4%)	
Morphine	1
Fentanyl	4
Sufentanil	2
Colloids (*n*=13, 2.7%)	
Gelatin	11
Hetastarch	2
Other agents (*n*=14, 2.9%)	
Propacetamol	4
Aprotinin	2
Chymopapain	2
Bupivacaine	1
Protamine	1
Ketoprofen	1
Hyaluronidase	1
Methylene blue	1
Ethylene oxide	1

In five patients, careful assessment of the medical history revealed the onset of an adverse reaction during a previous anaesthetic. In three cases, no allergic investigations had been performed after the initial incident. In the two remaining cases, diagnosis of sensitization to a neuromuscular blocking agent had been made after the initial incident.

Clinical features

Most adverse reactions were grade II (22.9%) or grade III (62.6%); only 10.1% were grade I and 4.4% grade IV. Cutaneous symptoms were present in 69.6% of cases (*n*=332), angio-oedema in 11.7% (*n*=56), bronchospasm in 44.2% (*n*=211), arterial hypotension in 17.8% (*n*=85), cardiovascular collapse in 53.7% (*n*=256), bradycardia in 2.1% (*n*=10) and cardiac arrest in 4% (*n*=19) (Table 2). Cardiovascular collapse was the sole feature in 40 cases, hypotension in 10 cases, bronchospasm in 15 cases and cutaneous symptoms in 37 cases. Angio-oedema never occurred in isolation.

Table 2 Clinical features of anaphylaxis during anaesthesia in 477 patients in France between January 1997 and December 1998

Clinical symptoms	Number of cases (%)	Sole feature (number of patients)
Cardiovascular symptoms		
Arterial hypotension	85 (17.8%)	10
Cardiovascular collapse	256 (53.7%)	40
Bradycardia	10 (2.1%)	
Cardiac arrest	19 (4.0%)	
Bronchospasm	211 (44.2%)	15
Cutaneous symptoms	332 (69.6%)	37
Angio-oedema	56 (11.7%)	

Bronchospasm was associated with a grade II reaction in 45 cases (21.3%), a grade III reaction in 159 cases (75.4%) and a grade IV reaction in seven cases (3.3%).

Severe complications, such as transient renal failure (*n*=2), coma (*n*=4), persistent vegetative state (*n*=1), hemiplegia (*n*=1) and neurological sequelae in the newborn of a pregnant patient *n*=1, were observed.

No differences in symptom severity were observed with respect to sex, history of atopy, asthma or food and drug intolerance. In eight cases, long-term treatment with β-blockers was noted. Seven of these cases were of grade III severity and one was of grade IV with cardiac arrest.

A significant association between the onset of bronchospasm and a history of atopy or asthma was observed ($P<0.005$).

Specific considerations for neuromuscular blocking agents and latex allergy

Neuromuscular blocking agents

The respective contribution of each neuromuscular blocking drug is shown in Table 1. Three hundred and thirty-six cases of anaphylaxis involved a neuromuscular blocking agent. Although succinylcholine (*n*=78) remains a major causal agent, rocuronium (*n*=98) was the drug incriminated most frequently over the 2 yr (1997–1998) study period. Atracurium (*n*=71) and vecuronium (*n*=59) were also involved frequently, whereas reactions to pancuronium (*n*=20), mivacurium (*n*=9) and cisatracurium (*n*=1) were less common. When considering these results, the actual clinical use of these drugs in France should be taken into account. This can be estimated on the basis of the results of the survey of the market share of neuromuscular blocking agents. The percentages of vials of each drug used in operating rooms and in intensive care units were also considered (Table 3). A correction factor based on the average number of vials used during anaesthesia in one patient, defined with and accepted by the principal manufacturers of neuromuscular blocking agents (Glaxo Wellcome and Organon Teknika) was also used to estimate the number of anaesthetized patients exposed to each

Table 3 Patient exposure to the various neuromuscular blocking agents and number of reactions observed between January 1997 and December 1998 in France (n=336) *Data obtained from Le Panel Hospitalier, MAPI (Lyon: Edition Domaine Medical, 1998) and from pharmaceutical companies †Established in collaboration with pharmaceutical companies using a correction factor taking into account the average number of vials used for one patient during an anaesthetic

	Market share in anaesthesia (vials, %)*	**Patients exposed (%)†**	**Anaphylactic reactions 1997–1998**		**Ratio % reactions/% patients exposed**
			Number	**(%)**	
Succinylcholine 100 mg/10 ml	6.5	7.6	78	23.2	3.05
Rocuronium 50 mg/5 ml, 100 mg/10 ml	8.6	10	98	29.2	2.92
Vecuronium 4 mg/1ml, 10 mg/1 ml	17.5	11.5	59	17.6	1.53
Pancuronium 4 mg/2 ml	7	3.3	20	5.9	1.78
Atracurium 25 mg/2.5 ml, 50 mg/5 ml	51.2	60.0	71	21.1	0.35
Mivacurium 10 mg/5 ml, 20 mg/10 ml	7	5.4	9	2.7	0.5
Cisatracurium 20 mg/10 ml, 5 mg/2.5 ml, 10 mg/5 ml	1.4	1.7	1	0.3	0.17
Gallamine 40 mg	0.8	0.5	–	–	–
	100%	100	336	100%	

compound. A significant difference was observed when percentage of anaphylactic reactions to each drug was compared with the estimated percentage of patients who received these drugs over the same time period (P<0.0001). Succinylcholine and rocuronium appeared to be involved most frequently, followed by vecuronium and pancuronium, and atracurium was involved least frequently.

A significant female predominance was observed in reactions to neuromuscular blocking drugs [female, n=248 (73.81%); male, n=88 (26.19%); P<0.0001]. The distribution according to age range and sex is shown in Fig. 2A. No difference was observed in relation to sex or age when the different neuromuscular blocking drugs were considered.

A difference in the severity of the reactions was observed when neuromuscular blocking drugs and latex were compared (P<0.0001) (Fig. 3). Reactions to neuromuscular blocking drugs were of grade I in 7.0%, grade II in 21.0%, grade III in 67.1% and grade IV in 4.9% of patients. They appeared to be more severe than reactions to latex, which were of grade I in 25.9%, grade II in 27.8%, grade III in 44.4% and grade IV in 1.9%.

A history of one or more previous anaesthetics was obtained in 326 out of 336 cases. Detailed anaesthetic notes were available only rarely or not at all. Anaphylaxis was observed in 48 patients (14.7%) who had no history of anaesthesia or previous exposure to neuromuscular blocking agents.

Early plasma histamine and tryptase determinations were performed in 90 and 97 cases respectively. They were considered to be positive in 81 and 94 cases respectively. When both tests were performed in a patient, they were both negative in only two cases. This corresponded to a positive intradermal reaction to atracurium at a dilution of 10^{-3}.

The numbers of positive intradermal test results according to the dilution threshold and the different agents involved are summarized in Table 4. Skin tests were performed in 331 out of 336 patients. They were negative in four cases. In each of these four cases, the severity grade of the reaction was III or IV, and specific IgE against a neuromuscular blocking agent was detected. Moreover, tryptase determination was positive in three of them.

Cross-reactivity to the muscle relaxants commercially available in France was tested in 317 cases. Cross-sensitivity was observed in 262 cases (82.6%). The highest rate of cross-reactivity was observed with rocuronium (89.4%) and vecuronium (92.7%); it was 72.6% for succinylcholine.

Specific IgE assay was performed in 234 patients. Results for the various agents studied are summarized in Table 5. They were positive in 202 cases (86.3%). Negative results for both IgE and skin tests were never observed. In the four cases of life-threatening reaction and negative skin tests, the IgE assay was positive, with a high percentage of specific IgE binding in the presence of the offending molecule.

Latex

Fifty-nine cases of latex anaphylaxis were reported during the study period. A significant female predominance was observed [female, n=43 (72.9%); male, n=16 (27.1%); P<0.001]. The distribution according to age range is shown in Fig. 2B. This distribution was significantly different from those observed with neuromuscular blocking agents (P<0.0001), for which the incidence was higher in the younger age ranges.

Reactions to latex were less severe than those observed with neuromuscular blocking drugs (P<0.0001) (Fig. 3). On four occasions, these reactions occurred during gynaecological procedures, after injection of oxytocin, and in one case after removal of a tourniquet.

A history of previous anaesthesia was found in 51 of the 59 cases of latex allergy (86.4%). No detailed information was available about the number of previous anaesthetics or the patients' occupational status. A history evocative of latex sensitization, such as fruit allergy or intolerance to materials containing rubber latex, was noted retrospectively in 14 cases (23.7%). Atopy was present in 23 cases (39%) and asthma in seven (11.9%).

Skin prick tests were performed in 58 out of 59 cases and were positive in 57 patients (98.3%). In the patient with a negative skin test and the patient not investigated using the prick-test, IgE latex-specific assay was positive. Specific latex IgE assay was performed in 41 of these patients. It was positive in 38 cases (92.7%).

Discussion

This study represents one of the largest surveys ever published of the incidence of anaphylaxis during anaesthesia over a 2-yr period. Diagnosis was established on the basis of systematic skin testing of the various suspected agents combined with widespread use of specific IgE assays. Nevertheless, this survey underestimates the real picture,

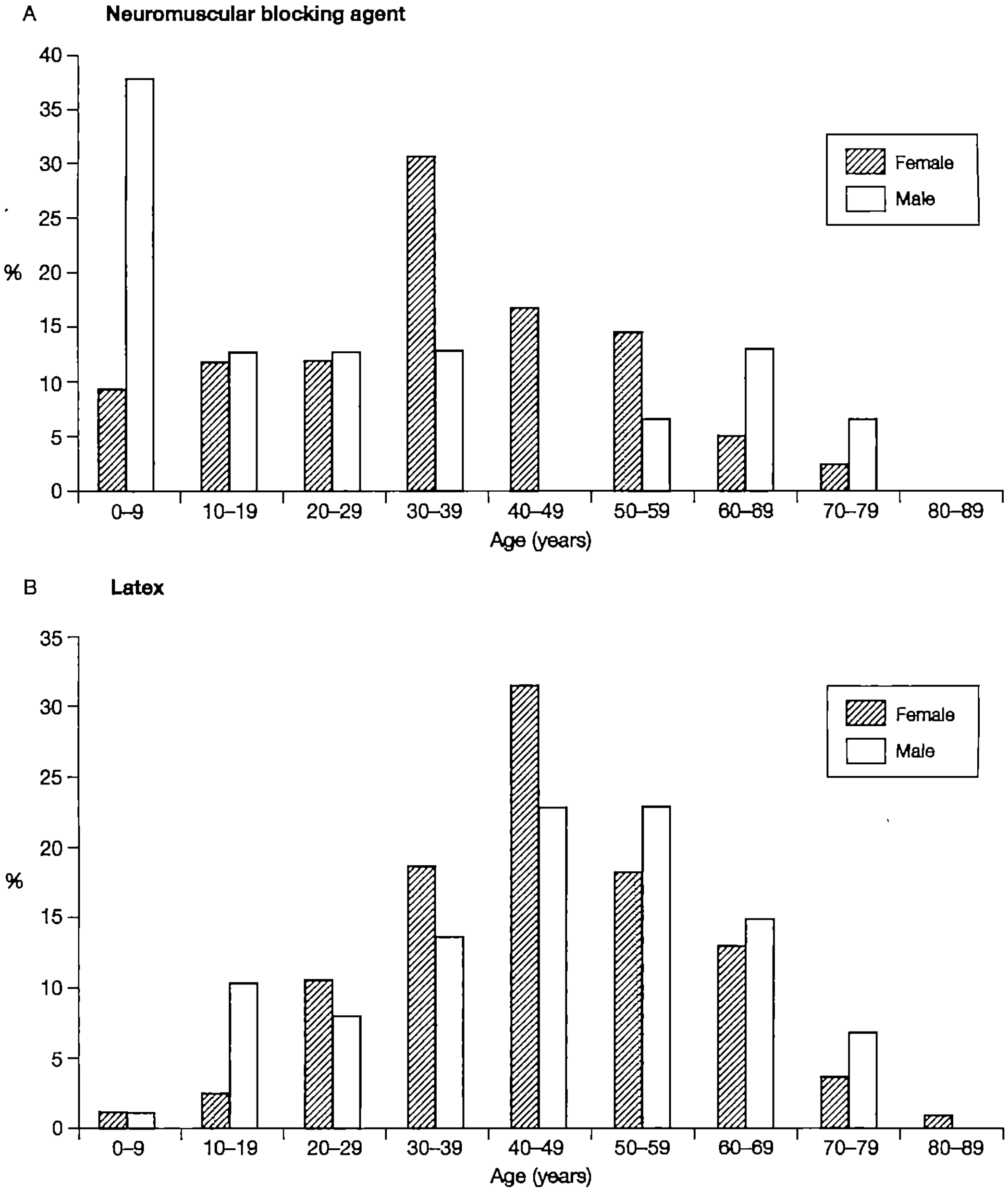

Fig 2 Distribution according to age range of anaphylactic reactions to (A) neuromuscular blocking agents (males n=88, females n=248) and (B) latex (males n=16, females n=43), in France between January 1997 and December 1998.

because it has been demonstrated that in France 30–40% of patients presenting with anaphylactoid reactions during anaesthesia did not have further allergic work-up.[21] Moreover, some patients who had experienced an adverse reaction during an anaesthetic might have been investigated in centres other than those involved in this study.

Our results confirm the large female predominance (2.7 female/1 male) of anaphylactic reactions, although it is less marked than that reported in other studies, where it ranges from 8 females/1 male[22] to 3.5 females/1 male.[9] It should be noted that this difference persists even when the sex ratio of anaesthetized patients established by the French survey of anaesthesia (1.1 female/1 male) is taken into account.[20]

Atopy and the presence of drug or food intolerance were assessed by history. Immunological assessment by skin testing or immunoassay was not performed systematically. The presence of atopy was reported in 25.4% of our patients. This rate is similar to that observed in our previous survey[2] and that observed in normal subjects.[23] However, as reported previously,[2 24] the presence of atopy was significantly more frequent in cases of latex allergy than in allergy to neuromuscular blocking agents (39 *vs* 24.8%, $P<0.01$). A history of drug allergy was present in 15.9% of our patients, a rate that approaches that reported in normal subjects (15%).[25] In most cases, clinical reactions were severe (90% of cases were at least grade II) and often life-threatening (67% were grade III or IV). These results confirm the severity of immune-mediated adverse reactions. This contrasts with reports of anaphylactoid reactions of a non-immune type, 49% of which were of grade I.[2] In addition, it should be noted that, because of the design of the present study, severe reactions resulting in death or major clinical sequelae impeding patient follow-up remained unaccounted for. Clinical observations in which tryptase was determined post-mortem[26] or specific muscle relaxant IgE was detected in blood samples taken during a fatal anaesthetic anaphylactic event[3] have been reported.

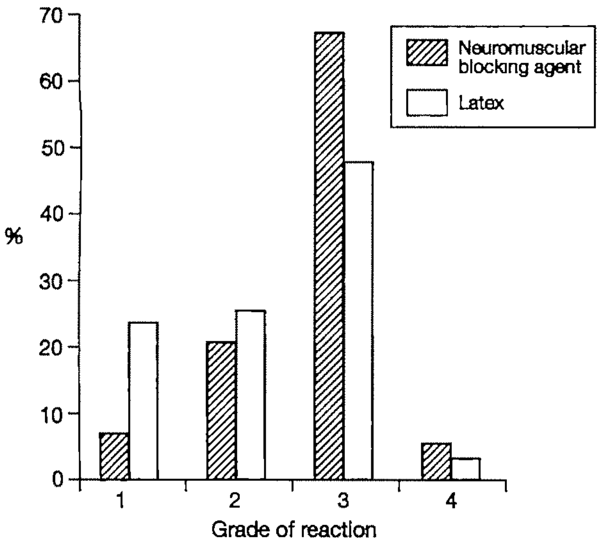

Fig 3 Frequencies of clinical severity grades of anaphylactic reactions to neuromuscular blocking agents (n=336) and latex (n=59) in France between January 1997 and December 1998

The most common features in this study were cardiovascular manifestations, present in 71.47%, followed by cutaneous symptoms (69.6%) and bronchospasm (44.2%). Cardiovascular symptoms were the sole feature in 10.5% of cases and in 10 cases were limited to hypotension. Similarly, bronchospasm was the only sign in 15 cases. These results concur with previous data[2 16 27] and may explain why the reaction can be attributed to causes other than anaphylaxis. As in previously reports, asthmatic patients with anaphylaxis often presented with bronchospasm.[16 27] Reaction severity was more pronounced in cases of sensitization to neuromuscular blocking agents than in cases of latex sensitization.[2]

The overall distribution of the various causal agents was similar to those reported previously.[2 27] Anaphylactic reactions to local anaesthetics appear to be uncommon.[16] Adverse reactions to colloids were less frequent than in some previous studies[27]. This probably reflects the decreased use of gelatins as volume expanders in France. Latex sensitization was involved in 12.1% of cases. These results differ significantly from previous reports from a time when latex allergy was poorly recognized.[9] The relative decrease in the number of cases diagnosed is encouraging;

Table 4 Intradermal skin test results according to the neuromuscular blocking agent involved in the anaphylactic reaction (n=331)

Neuromuscular blocking agent	**Skin test positivity threshold (number of cases)**					
	Dilution					
	10^{-1}	**10^{-2}**	**10^{-3}**	**10^{-4}**	**10^{-5}**	**10^{-6}**
Succinylcholine	1	24	20	11	2	2
Rocuronium	6	33	28	9	1	
Vecuronium	13	17	17	3	2	
Mivacurium		3	4	2		
Pancuronium	6	9	3			
Atracurium		16	37	9	1	
Cisatracurium				1		

Table 5 Results of IgE-specific assay according to the neuromuscular blocking agent involved in the anaphylactic reaction (n=234)

IgE	Positive	Negative
Succinylcholine	54	5
Rocuronium	68	5
Vecuronium	31	4
Pancuronium	10	1
Mivacurium	5	3
Atracurium	34	14
	202	32

in our last published survey latex allergy was involved in 16.6% of cases.[2] Increasing awareness of the risk of latex sensitization in spina bifida children[28] or health-care workers,[29] combined with the efficacy of surgical procedures in a latex-free environment,[30] could be responsible for the decrease in the incidence of latex anaphylaxis we observed.

Although succinylcholine (n=78) remains a major causal agent, there are differences in this report, compared with our last survey, in the involvement of other neuromuscular blocking agents.[2] Rocuronium (n=98) appears to be the agent involved most frequently. As can be seen in Table 3, when account is taken of differences in the anaesthesia market share and the number of patients exposed, there are significant differences among the drugs that have been incriminated. These observations rely on the estimation of the number of patients exposed and should therefore be considered with circumspection. In addition, anaesthetists might have paid more attention to the effects of the drugs that have become available more recently, especially in cases of mild reactions. However, the increasing awareness of adverse reactions to rocuronium and the incidence of anaphylaxis (82 cases) is noteworthy.[2 27 31-38]

In our study, positive diagnosis was mainly based on clinical history and skin test results, often corroborated by specific IgE assay. Although skin tests have been used extensively for more than two decades, there has been controversy recently concerning their use in the diagnosis of sensitization to rocuronium.[39] According to Levy and colleagues,[39] rocuronium prepared as a solution of 10 mg ml^{-1} requires dilution to 10^{-2} to avoid false-positive intradermal test results. This differs from the 10^{-1} dilution recommended by the Commission Tripartite en Allergologie, which was the highest test concentration used by our participating centres.[17] However, in the report of Levy and colleagues, intradermal testing was performed on the anterior face of the forearm rather than on the patient's back. The latter approach is favoured in France because the skin of the forearm is more likely to release histamine non-specifically.[15] Moreover, an unexpected mean weal diameter of almost 6 mm with a negative control injection of saline was reported by Levy and colleagues. According to the Commission Tripartite en Allergologie recommendations, such a result would have invalidated the test. Among the 98 cases of sensitization to rocuronium we observed, intradermal testing was considered positive at a dilution of 10^{-1} in only six cases. These observations corresponded to three grade II and three grade III reactions, and in all of these cases the specific IgE assay against rocuronium was positive.

Nevertheless, the differences observed in the relative frequencies of sensitization to the various commercially available neuromuscular blocking agents remain to be explained. Indeed, one of the mechanisms of anaphylaxis to these drugs involves the presence of quaternary ammonium ions,[40] but other factors, such as the distance between the quaternary ammonium ions and the flexibility of the entire molecule, may also be important.[41] The differences observed in cross-sensitization between different agents in this study have also been noted in previous reports; cross-sensitization appears to be more frequent with aminosteroid neuromuscular blocking agents than with benzylisoquinoline-derived neuromuscular blocking agents.[42 43]

The need for early as well as delayed laboratory investigations to confirm the occurrence of anaphylaxis should be stressed. In this series, early histamine and tryptase determinations were performed in 90 and 97 cases of anaphylaxis due to a neuromuscular blocking agent, and were found to be positive in 81 and 94 cases respectively. Moreover, when both tests were performed in the same patient, they were both negative in only two patients. This is consistent with previous reports concerning the value of these tests in the diagnosis of anaphylaxis to anaesthetic drugs.[44 45]

Similarly, determination of specific muscle relaxant IgE, when performed, was positive in 86.3% of cases. These results were obtained with RIAs based on coupling an analogue of choline to Sepharose (QAS-RIA)[18] or *p*-aminophenylphosphorylcholine to agarose (PAPPC-RIA).[19] These RIA methods offer greater sensitivity (QAS-RIA, 87.5%; PAPPC-RIA, 97%) and specificity (QAS-RIA, 100%; PAPPC-RIA, 97%) than classic commercially available RIA kits, such as the RAST-succinylcholine test (sensitivity 66%).[18] In addition, when performed, specific latex IgE assays were positive in 92.7% of cases, confirming the quality of this RIA. These results support the widespread use of the specific IgE assay in suspected cases of adverse reactions to anaesthetics. Moreover, serum samples can be drawn at the time of the adverse reaction and stored for testing later. This can facilitate further investigation of fatal anaphylactic reactions.[3]

In conclusion, our study confirms the predominance of sensitization to neuromuscular blocking agents and latex in anaphylactic reactions during anaesthesia. The differences observed over time concerning the relative contributions of the various neuromuscular blocking agents strengthen the need for post-marketing risk detection for new drugs. In addition, our results underline the need for wider use of specific IgE assays combined with skin testing in the diagnosis of sensitization to neuromuscular blocking agents and latex, even in cases of minor adverse reactions. As suggested by the reduced incidence of anaphylaxis to latex, which is a probable consequence of generalized identification and preventative measures, an active policy to identify at-risk patients through the establishment of allergo-anaesthesia centres should be promoted.

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Measuring the costs of inhaled anaesthetics†

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The cost of inhalation anaesthesia has received considerable study and is undoubtedly reduced by the use of low fresh gas flows. However, comparison between anaesthetics of the economies achievable has only been made by computer modelling. We have computed anaesthetic usage for MAC-equivalent anaesthesia with isoflurane, desflurane, and sevoflurane in closed and open breathing systems. We have compared these data with those derived during clinical anaesthesia administered using a computer-controlled closed system that measures anaesthetic usage and inspired concentrations. The inspired concentrations allow the usage that would have occurred in an open system to be calculated. Our computed predictions lie within the 95% confidence intervals of the measured data. Using prices current in our institution, sevoflurane and desflurane would cost approximately twice as much as isoflurane in open systems but only about 50% more than isoflurane in closed systems. Thus computer predictions have been validated by patient measurements and the cost saving achieved by reducing the fresh gas flow is greater with less soluble anaesthetics.

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Keywords: anaesthetic volatile, isoflurane; anaesthetics volatile, desflurane; anaesthetics volatile, sevoflurane; anaesthetics, audits

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The economies due to low-flow anaesthesia are undoubted,[1 2] but comparisons between anaesthetics have been made only by computer modelling[3] and have not yet been confirmed in clinical practice. Weiskopf and Eger[3] presented the predicted ratio of usage of two anaesthetics at equal MAC plotted against time for various fresh gas flows. This elegant technique enables a break-even line, determined by the relative expense of the anaesthetic liquids, to be plotted for any two anaesthetics using local institutional prices, but there are no data to allow comparisons with sevoflurane.

As a matter of principle, we believe that 'virtual-world' computer predictions should be tested with real data whenever possible, both to test the accuracy of the model and to determine physiological variability. We have established a database of measurements collected during closed system anaesthesia. For each patient, the rate of anaesthetic use and the inspired anaesthetic concentration have been recorded. These data allow us to compare the actual cost of different anaesthetics in closed breathing systems, to estimate the cost of different anaesthetics in non-rebreathing systems, and to test the predictions of computer models.

Methods

Computer predictions

A four-compartment patient was modelled using specially developed software, details of which are given in the Appendix. The usage of isoflurane, desflurane, and sevoflurane to achieve 1.3 MAC at 0.2, 1, 2, 4, and 6 litre min^{-1} was computed and plotted for the three possible pairwise comparisons according to the method of Weiskopf and Eger.[3]

Patient data

The computer predictions were compared with our database of patients anaesthetized using our completely closed, computer-controlled anaesthetic system.[4] Many of these patients contributed results to our previous publications,[5–7] and all gave written, informed consent with local Research

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† Part of this work was presented to the Plymouth meeting of the Anaesthetic Research Society, July 1999, and an abstract has appeared in the proceedings of that meeting (*Br J Anaesth* 1999; **83**. 524P).

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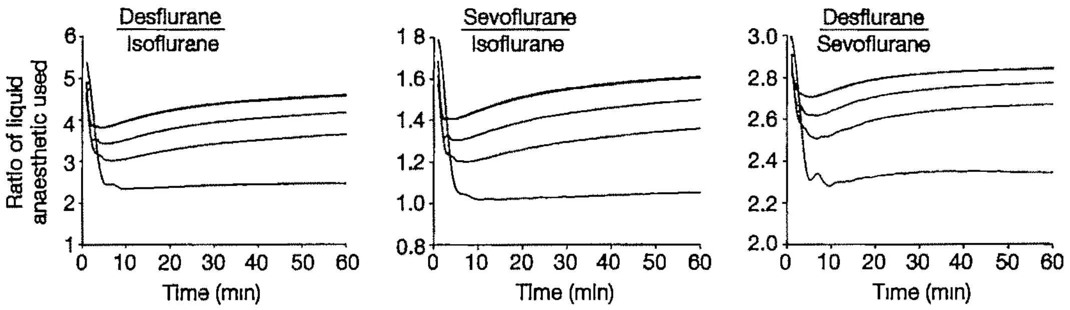

Fig 1 The ratio of cumulative liquid anaesthetic use at different fresh gas flows predicted by a computer model. In each plot the curves represent, from top to bottom, a fresh gas flow of 4, 2, 1, and 0.2 litre min^{-1}. The non-rebreathing case was indistinguishable from the 4 litre min^{-1} case

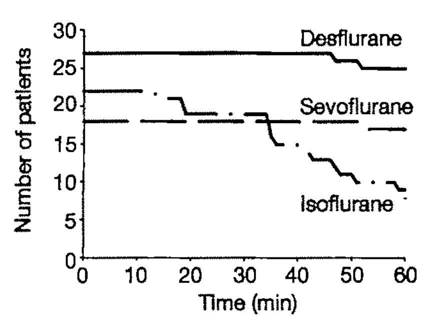

Fig 2 The number of patients contributing to the clinical data shown in Figures 3–5

Ethics Committee approval. All patients received controlled ventilation to maintain their end-expired $P\text{CO}_2$ at 4.5–5 kPa. The system maintained end-expired concentrations of 1.5% isoflurane, 8% desflurane, or 2.4% sevoflurane by injection of liquid anaesthetic into the system. These were intended to represent 1.3 MAC for each agent, but in view of a recent meta-analysis,[8] which recommended a value of 6.6% for desflurane MAC, the values of usage and inspired concentrations of desflurane for each patient were increased by 10%. The rate of anaesthetic usage in the closed system was measured directly by this breathing system. The rate of usage that would have occurred in an open system was estimated by multiplying a fresh gas flow of 6 litre min^{-1} that would have been necessary by the measured inspired anaesthetic fraction and converting to volumes of liquid at 20°C.[9]

Statistical analysis

There are two problems to be addressed. First, although we know the inter-patient variability of anaesthetic usage, we do not know the variability when individual patients are administered anaesthetics repeatedly. Anaesthetic usage is very variable between patients and so the variability of the ratio of usage of two anaesthetics in different patients will be huge, making agreement between modelling and experiment undemanding. However, we expect that a patient who had a large isoflurane usage would have had a large desflurane or sevoflurane usage if they had been used instead. We have assumed arbitrarily that half the overall variability in the usage of each anaesthetic is because of within-patient variability and half because of between-patient variability.

The second problem is that variability in the ratios of random variables, and confidence intervals around a central value, cannot in general be calculated exactly.[10] We have undertaken Monte Carlo simulations of this problem, generating sets of artificial results as if from 1200 patients for each anaesthetic.[11] The anaesthetic usage for the *i*th data set at each time point t was given by $u_i(t)=\mu(t)+\varphi_i\sigma(t)/\sqrt{2}$, where $\mu(t)$ and $\sigma(t)$ are the mean and SD of the measured usages at time t, φ_i is a random normal deviate, different for every artificial patient and every anaesthetic, and the $\sqrt{2}$ factor allows for the fact that half the population variance is assumed to be a result of within-subject variation. For each pair of anaesthetics, 1200 values of the ratio of usage were then calculated at each time point, enabling 95% confidence intervals to be determined numerically.

Results

The computer predictions of anaesthetic usage at different fresh gas flows are shown in Figure 1. The number of patients whose results were used for analysis are shown in Figure 2. Most of the patients in the isoflurane group were from our initial study of procedures lasting only an hour or so;[5] longer data sets are available for desflurane[6] and sevoflurane.[7] There was instability in the rate of anaesthetic usage for the first few minutes as the target end-expired concentration was established, resulting in large variability of both the measured variables. After 5 min the SD calculated from the Monte Carlo experiments reduced to a value within 1% of an estimate of the SD of the ratio of two random variables that is said to be valid when variance in the denominator is small.[10] The lower and upper 95% confidence intervals were then approximately −1.7 and +2.3 SD, respectively, from the mean value. These limits are drawn from our patient data and show the range within which the results of a randomly chosen patient would be expected to lie. The computed results are shown against

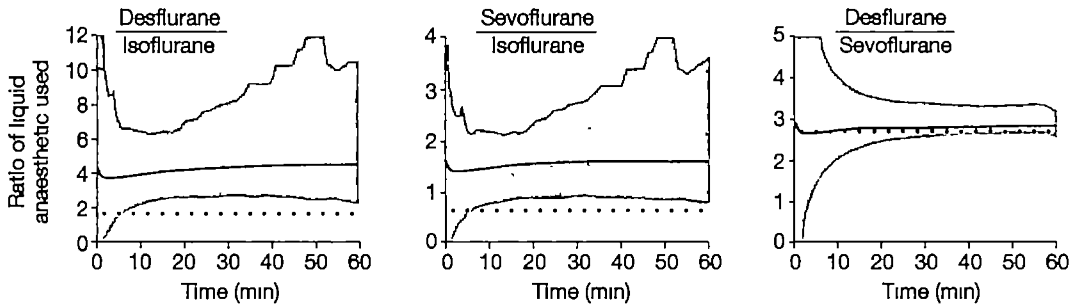

Fig 3 The shaded area shows the 95% confidence interval of the ratio of usage of anaesthetics in an open system. The continuous lines are the predictions of the computer model. The break-even lines for our institution are dotted and these lines should be adjusted to local costs. When the ratio of usage lies below this line then the anaesthetic in the numerator of the ratio is the less expensive

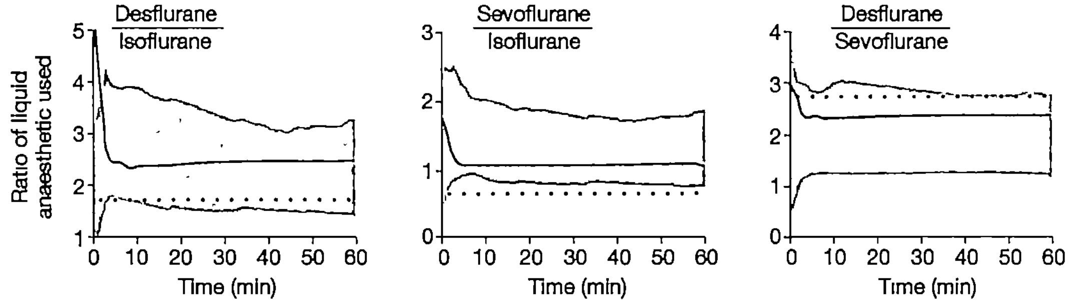

Fig 4 The shaded area shows the 95% confidence interval of the ratio of usage of anaesthetics in a closed system. The continuous lines are the predictions of the computer model. The break-even lines are dotted and these lines should be adjusted to local costs. When the ratio of usage lies below this line then the anaesthetic in the numerator of the ratio is the less expensive.

these 95% confidence intervals of the patient results for the open system in Figure 3 and for the closed system in Figure 4. These figures also show the break-even lines at our institution, which are at 1.7, 0.62, and 2.7 for isoflurane: desflurane, isoflurane:sevoflurane and sevoflurane:desflurane, respectively.

Discussion

The accuracy of the computer simulation is supported by the patient data. Comparison with Weiskopf and Eger's original paper shows little difference between the model they used, based on 'artificial' pharmacokinetic compartments derived from Yasuda's study of elimination kinetics,[12] and the model we have used based on Eger's original and 'natural' physiological compartmental model,[13] allowing for the fact that we have taken a different value for the MAC of desflurane. This does not confirm that either represents patient uptake accurately, for if predicted usage was systematically in error, even in a time-dependent fashion, then the ratio of usage of two anaesthetics would be unaffected. In fact, the usage predicted by our model matches the clinical data (Fig. 5), so we conclude that it is good enough to be used as a guide to clinical expectation and that the computer-generated data in Figure 1 for flows other than open and closed systems are also likely to be correct.

We have no data on within patient variability of anaesthetic uptake. If it is less than our assumed value of half the total variability, then the confidence intervals shown in Figures 3 and 4 overstate the variability in the ratios of anaesthetic usage. The distribution of ratios is a troublesome problem in statistics for the variance may not be defined and, in general, only an approximate solution is available.[10] We used a Monte Carlo simulation to produce a better estimate of the variance of our data and found that the use of the approximation would have underestimated variance, particularly for the early data but also when the number of patients in the isoflurane group was small. In spite of these efforts to be stringent, our conclusions are inevitably weakened by our arbitrary specification of within-patient variance.

Although the cost of drugs is a small part of the anaesthetic budget and an even smaller part of the total cost of an operation, many anaesthetists find it worthwhile to have some idea of comparative costs when planning their practice. We interpret our results as saying that when a patient is anaesthetized at our institution with an open system, isoflurane is almost certain ($P>0.95$) to be much less expensive than desflurane and sevoflurane, and that

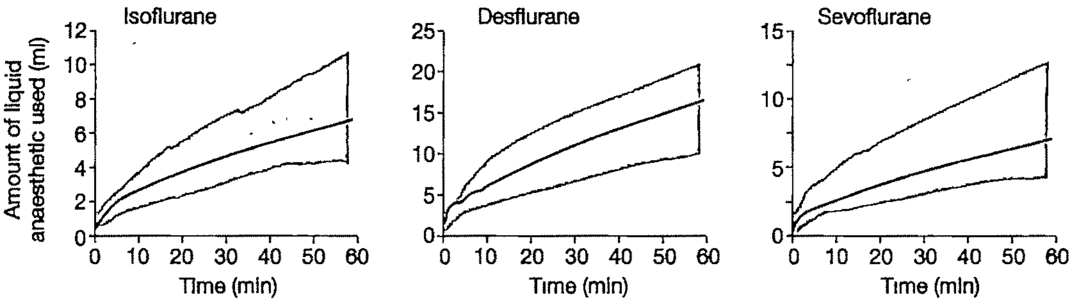

Fig 5 The shaded area shows the 95% confidence interval of the usage of anaesthetics in a closed system. The continuous lines are the predictions of the computer model.

Table 1 Computer model parameters The patient weighed 70 kg, cardiac output 5000 ml min^{-1}, minute ventilation 5000 ml min^{-1}, 35% dead space, 5% right-to-left shunt, 15% left-to-right shunt, all constant during the simulations. Solubility data have been drawn from Zhou and colleagues.[16] [17]

	% Body weight	% Non-shunted cardiac output	$\lambda_{tissue/gas}$		
			Iso	des	sev
Blood	–	–	1.38	0.55	0.68
Vessel rich group	9	75	2 5	0.6	1.1
Muscle group	50	18	2.1	0.8	1 3
Vessel poor group	19	2	2.1	0.8	1 3
Fat	22	5	70.5	15.3	40 6

sevoflurane would cost the same as desflurane. If a closed system is used, isoflurane is almost certain to be less expensive than sevoflurane and would probably ($P>0.5$; $P<0.95$) be less expensive than desflurane, but desflurane would probably be a little less expensive than sevoflurane. Not only are the absolute costs of all the anaesthetics less in closed systems, but the relative cost differences are also reduced. The position of the break-even line will change as prices vary with time and between institutions, but the ratios of usage shown in Figures 3 and 4 are invariable and can always be used to determine relative expense.

Appendix

Narkup was a simple program, predicting the uptake of anaesthetics using a four-compartment model.[14] It has been modified to make it run more accurately and efficiently over long simulations by integrating simultaneously variables representing all anaesthetics in all components of the model (from breathing system concentrations to tissue tensions), using a variable step length.[15] The user places an upper limit on the step size throughout which the fresh gas composition and patient physiology cannot be changed, because they must be constant during an integration step. The price paid for these improvements is that the delays built in to the original Narkup program to represent circulation times are no longer included and so blood volume is no longer considered as a separate compartment. This is of no consequence when considering events on a time scale of 1 h. The servo-control algorithms that are used by our automated anaesthetic breathing system form the basis of the servo-control algorithms in the new version of Narkup. The compartment parameters used in the computer experiments we have reported in this paper are listed in Table 1, and the integration step size was limited to a maximum of 10 s to mimic the speed of updating in the real system.

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Improvement of 'dynamic analgesia' does not decrease atelectasis after thoracotomy

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There is still controversy concerning the beneficial aspects of 'dynamic analgesia' (i.e. pain while coughing or moving) on the reduction of postoperative atelectasis. In this study, we tested the hypothesis that thoracic epidural analgesia (TEA) prevents these abnormalities as opposed to multimodal analgesia with i.v. patient controlled analgesia (i.v. PCA) after thoracotomy. Fifty-four patients undergoing thoracotomy (lung cancer) were randomly assigned to one of the two groups. Clinical respiratory characteristics, arterial blood gas, and pulmonary function tests (forced vital capacity and forced expiratory volume in 1 s) were obtained before surgery and on the next 3 postoperative days. Atelectasis was compared between the two groups by performing computed tomography (CT) scan of the chest at day 3. Postoperative respiratory function and arterial blood gas values were reduced compared with preoperative values (mean (SD) FEV_1 day 0: 1.1 (0.3) litre; 1.3 (0.4) litre) but there was no significant difference between groups at any time. PCA and TEA provided a good level of analgesia at rest (VAS day 0: 21 (15/100); 8 (9/100)), but TEA was more effective for analgesia during mobilization (VAS day 0: 52 (3/100); 25 (17/100)). CT scans revealed comparable amounts of atelectasis (expressed as a percentage of total lung volume) in the TEA (7.1 (2.8)%) and in the i.v. PCA group (6.71 (3.2)%). There was no statistical difference in the number of patients presenting with at least one atelectasis of various types (lamellar, plate, segmental, lobar).

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Postoperative analgesia may improve morbidity and clinical outcome.[1–3] However, the influence of analgesic techniques on atelectasis formation is still a matter of debate. Because of diaphragmatic dysfunction and pain, thoracotomy induces a severe postoperative restrictive syndrome. Compared with systemic opioids, thoracic epidural analgesia (TEA) allow patients to cough and breath deeply,[4] both measures that increase lung volume. Therefore, we hypothesized that atelectasis may be prevented by better 'dynamic' analgesia with TEA.

Patients and methods

The sample size for this study was based on atelectasis rates cited in previous studies.[5 6] The data suggested that a power of 95% for detecting a 50% difference in atelectasis at an alpha level of 0.05 would be obtained with 23 patients in each group. The study procedure was approved by the ethics committee of Nice University (CCPPRB, Nice) and 54 patients gave their informed consent. Patients were scheduled for thoracic surgery (lung cancer) by postero-lateral thoracotomy. A smoking history of more than 20 pack yr was required. Criteria of non-inclusion were immune depression (corticosteroid therapy or HIV infection), history of fever or infection, poor nutrition or obesity (body mass index (BMI) less than 18 or over 30), atelectasis of all types on systematic preoperative computed tomography (CT) scan and contraindication for TEA, i.v. patient-controlled analgesia (i.v. PCA), or non-steroidal anti-inflammatory drugs (NSAIDs).

Respiratory characteristics were determined by clinical examination, chest x-ray, arterial blood gas analysis and

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respiratory function tests (forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC)). The day before surgery, patients were randomized in one of the two groups of analgesia using a table of random numbers to receive either postoperative i.v. opioid PCA or epidural ropivacaine–sufentanil (TEA).

All patients were premedicated with 100 mg oral hydroxyzine and were given 1.5 g cefuroxime 1 h before and for 24 h after surgery (750 mg every 8 h). In the TEA group, a 20-gauge catheter (Vygon, Les Ulis, France) was inserted 3–4 cm into the epidural space after midline puncture at T4–T5 with a Tuohy needle (Braun, Melsungen, Germany). Good position was defined by bilateral anaesthesia between T1 and T8 after injection of 3 ml of 2% lidocaine with 1/200 000 epinephrine *via* the epidural catheter. If the catheter could not be inserted or was accidentally withdrawn before day 3, the patient was given an i.v. PCA pump, but was kept in the TEA group for the intention to treat analysis.

General anaesthesia was standardized in groups. Induction was achieved with thiopental 5 mg kg^{-1}, sufentanil 0.5 $\mu g\ kg^{-1}$, and atracurium 0.5 mg kg^{-1}. After tracheal intubation with a left side double lumen endobronchial tube (Carlens®, Rüsch, Germany) (39 French women, 41 French men) the lungs were ventilated by a volume-cycled ventilator (Cato®, Dräger, Germany) at zero end-expiratory pressure, with a tidal volume of 10 ml kg^{-1}. The rate was adjusted to maintain an end-tidal carbon dioxide partial pressure near 35 mm Hg. After checking clinically that ventilation of the operative lung had ceased, anaesthesia was maintained with 0.5–1 MAC sevoflurane and 70–80% oxygen in air, with the same ventilatory parameters maintained during one lung ventilation. Continuous infusion of atracrium 0.6 mg $kg^{-1}\ h^{-1}$ and sufentanil 0.3 $\mu g\ kg^{-1}\ h^{-1}$ was also maintained. Central body temperature and urinary flow were monitored. Invasive arterial pressure was monitored with a radial catheter inserted under general anaesthesia and a central venous line measured central venous pressure. At the end of surgery, the upper lung was re-expanded by manual inflation under visual control with 50% nitrous oxide–oxygen. The final inflation was performed at Paw=40 cm H_2O for 5 s. Patients were warmed until body temperature reached 36°C. When clinical signs of weaning were present, patients were extubated and oxygen administered via a nasal probe, adapted to pulse oximeter values (3–6 litre min^{-1}). Patients were placed in the PACU for 4 days.

Patients in the TEA group received an epidural continuous infusion of ropivacaine 0.2% combined with sufentanil (1 or 0.5 $\mu g\ ml^{-1}$ if age was over 70 yr). An infusion started 1 h before the end of surgery at a rate of 6 ml h^{-1}, and was adjusted thereafter according to the visual analogue scale (VAS). In the recovery room, i.v. PCA patients received an initial i.v. bolus administration of morphine (3-mg doses every 5 min) titrated by a nurse until VAS was lower than 40 mm. At this time, a PCA pump (Abbott Pain Manager®, Abbott Laboratories, North Chicago, IL, USA) was connected using a 1.5 mg bolus and a 5 min lockout period. If pain control was considered insufficient (i.e. VAS greater than 40 mm) analgesia rescue doses were given and repeated until efficient analgesia was achieved. In the i.v. PCA group, patients received a supplemental morphine 3 mg bolus every 5 min and in the TEA group, patients were given a supplemental bolus of ropivacaine 6 ml and continuous infusion was increased by steps of 2 ml h^{-1} every 30 min if needed. Patient monitoring and treatment of hypotension, nausea, vomiting, and pruritus were standardized. In case of hypotension (defined as systolic arterial pressure lower than 90 or 100 mm Hg in patients with arterial hypertension history), patients were given boluses of ephedrine from 3 to 30 mg titrated to achieve values over 100 mm Hg. For nausea, droperidol 2.5 mg was given i.v. every 4 h as needed, followed by ondansetron 4 mg if control was insufficient or if vomiting occurred. For itching, propofol 10–20 mg was given i.v. every 6 h as needed. All patients received propacetamol 2 g, an injectable acetaminophen prodrug, every 6 h, and 300 mg per 24 h continuous infusion of ketoprofen for 3 days. Patients were encouraged to use the PCA as often as needed and before physiotherapy.

Physiotherapy was performed twice a day by the same physiotherapist, according to a standardized 20-min procedure: abdominal and diaphragmatic breathing, deep breathing exercises and effective coughing. All patients received terbutalin aerosol just before physiotherapy. Patients were maintained in a semirecumbent position, and sat in an armchair the day following surgery.

Characteristics of patients were noted as well as factors influencing respiratory function, for example, smoking habit (pack yr), current or past-smoker (i.e. patients who stopped smoking for more than 8 weeks).[7] All patients received respiratory physiotherapy for almost 3 days preoperatively. Type of lung resection, duration of lung separation and anaesthesia, blood transfusion and volume of fluid infused during surgery were also noted. Blood gas analysis was performed daily at 07:00 in ambient air for 15 min, as well as a respiratory function test in a sitting position (Flow Meter®, Sherwood Medical, St Louis, MO, USA), measuring FVC and FEV_1. The physician performing the respiratory function tests was blinded to the study group. The best of three measurements was retained for analysis.

Chest x-ray was performed immediately after extubation. Thoracic CT scan was performed on the third day after the surgery (ELITE®, Epscint, IL, USA). All patients were placed in the supine position with arms above the head. Images were obtained from lung apex to costodiaphragmatic angle without i.v. infusion of contrast. Scans were obtained after inspiration of an ordinary tidal volume (acquisition time=1.1 s per section, tube current=240 mA and 140 KVp, matrix 512×512). The slice thickness was 10 mm with a 20 mm interval. Some 1 mm thick slices were obtained in patients with atelectasis. The dorsal border of atelectasis was manually highlighted. The ventral border between atelectasis and normal lung tissue was evaluated. The exact amount of atelectasis was calculated as the sum of all pixels (picture elements) having a density between −100 and +100 Hounsfield units.[8] Absolute lung area was calculated for each scan as atelectatic and aerated areas. The extent of atelectasis was expressed in square centimetres as a percentage of the total lung area. Atelectasis was also classified into four types depending on thickness: lamellar atelectasis <3 mm, plate atelectasis >3 mm and <10 mm, segmental atelectasis >10 mm and lobar atelectasis.[9]

Clinical complications were assessed daily. A chest x-ray was performed and analysed by a radiologist in case of tachypnea over 20 breaths min^{-1} associated with an arterial oxygen partial pressure below 60 mm Hg despite 6 litre min^{-1} oxygen and fever (above 38.5°C). Clinical respiratory complications were classified in two groups: (1) atelectasis with clinical intolerance requiring bronchial clearing by fibroscopy (CT scan was performed just before the fibroscopy) and (2) pneumonia (modified criteria of Andrews).[10]

Patients assessed pain using VAS ranging from 0 (no pain) to 100 mm (worst pain imaginable) at rest and while coughing every 4 h. All patients were instructed how to use the VAS preoperatively. Side effects arising from the analgesic procedure were also recorded. General effects including hypotension (systolic arterial pressure <90 mm Hg or 100 if hypertension history), heart rate, sedation (0=awake, 1=sleepy but awakened by oral order, 2=sleepy but awakened by nociceptive stimulation, 3=not responsive), respiratory depression (respiratory rate less than 8 breaths min^{-1}), confusion, nausea, vomiting, and pruritus, were recorded at 4-h intervals for 4 days. Lower limb motor block was assessed twice a day with the Bromage score (0=no paralysis; 1=unable to raise the leg, 2=enable to bend the knee, 3=paralysis). Local complications were also sought, including neurological complications, catheter occlusion, kinks, and displacement.

On the fourth day, the epidural catheter was withdrawn, and bacteriological analysis performed. At the end of the study, global satisfaction concerning pain was evaluated on a VAS (0 mm=not satisfied; 100 mm=entirely satisfied).

The perioperative characteristics were compared using chi-squared analysis for category and the Kruskall–Wallis test for continuous variables. The overall incidence of atelectasis in the two groups was compared with chi-squared analysis, whereas the percentage of atelectasis was evaluated with a Wilcoxon test. Postoperative assessment for all variables measured over time was evaluated using repeated measures analysis of variance. Results are presented as mean (SD). A significance threshold of $P<0.05$ was retained.

Results

Fifty-four patients were randomly assigned to one of the two groups of the study. Four patients were excluded: two in the i.v. PCA group (one atelectasis because of twist of the middle lobe diagnosed early at day 1, one myocardial infarction at day 2), two patients in the TEA group (one lung exclusion over 2.5 h because of difficult surgical procedure with postoperative lobar atelectasis diagnosed on chest x-ray just after extubation, one cardiac failure because of atrial arrhythmia). Statistical analysis, therefore, concerned 50 patients (i.v. PCA *n*=25, TEA *n*=25). Characteristics and preoperative respiratory evaluation tests were comparable in the two groups (Table 1). Accidental withdrawal of the epidural catheter before day 3 occurred in two patients and these were given an i.v. PCA pump.

The number of patients with lobar or infralobar atelectasis was comparable in the two groups (Table 2). The amount of atelectasis (expressed as a percentage of total lung volume) observed on the CT scans (mean (SD) [range]) did not differ significantly in the patients with TEA 7.1 (2.8) (0–28) i.v. PCA 6.71 (3.2) (0–31 i.v.)%. These data provided a 99% chance of detecting a 2% difference in atelectasis surface at an alpha level of 0.05. Two patients in each group developed poor respiratory function before day 3, and had a CT scan before any treatment (bronchial fibroscopy for atelectasis, or mechanical ventilation). Two patients in the TEA group, and one in the i.v. PCA group developed documented pneumonia requiring re-intubation and mechanical ventilation. The overall incidence of clinical respiratory complications was 14% (i.v. PCA: *n*=4; TEA: *n*=3). Three patients (all right pneumonectomy) died following these complications (6%), two in the TEA group, and one in the i.v. PCA group.

Compared with the preoperative value, FEV_1 decreased by 56% in the i.v. PCA group ($P<0.05$) and 44% in the

Table 1 Perioperative data and preoperative respiratory characteristics of patients. Values are mean (SD). Differences between the two groups were not statistically significant

	PCA	TEA
Patients (*n*)	25	25
Age, yr (SD) [range]	63.3 (11) (51–78)	64.8 (9) (47–81)
ASA status (1, 2, 3)	9/16/0	15/9/1
Sex (M/F)	20/5	21/4
BMI (kg m^2)	23.7 (3 3)	23.8 (2.9)
Current smokers (%)	52	56
Tobacco consumption (pack yr)	59 8 (21)	50.4 (20)
Preoperative physiotherapy (days)	6.6 (4 2)	6.1 (4.3)
Preoperative FEV_1 (litre)	2 5 (0 5)	2 3 (0 8)
Preoperative FEV_1 (% norm)	85.6 (3.1)	80 8 (19 9)
Preoperative FVC (litre)	3.3 (0.6)	3.4 (0.7)
Preoperative FVC (% norm.)	90 (12 4)	91 (24 3)
MMEFR 25/75 (% norm)	57.7 (31.2)	45 6 (25.7)
Preoperative Pa_{O_2} (mm Hg)	84.1 (7.2)	82.3 (8)
Preoperative Pa_{CO_2} (mm Hg)	39 4 (3)	39 (2.8)
Lobectomy (*n*)	15	16
Pneumonectomy (*n*)	10	9
Packed red blood cells (*n*)	3	2
Duration of anaesthesia (min)	184 (26)	176 (28)
Duration of one-lung-ventilation (min)	124 (26)	116 (28)
Perioperative fluid infusion (litre 24 h^{-1})	2.32 (0.23)	1.88 (0.44)

Table 2 Number of patients with at least one atelectasis of each type, assessed by CT scan. Values are expressed in numbers and percentage of patients Differences between the two groups were not statistically significant

	Lamellar	**Plate**	**Segmental**	**Lobar**
PCA (n=25)	12 (48%)	9 (36%)	5 (20%)	2 (8%)
TEA (n=25)	14 (56%)	9 (36%)	8 (32%)	2 (8%)

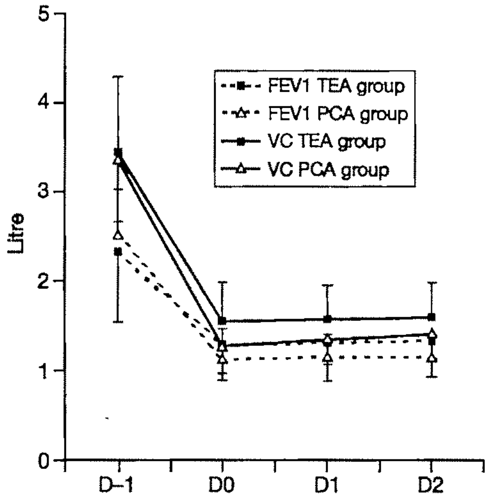

Fig 1 Spirometry values in both analgesic groups before and after surgery VC=vital capacity; FEV1=forced expiratory volume in 1 s; TEA group=group of patients with epidural analgesia. D-1=preoperative day 1; D0=recovery room; D1=first postoperative day. Values are mean (SD).

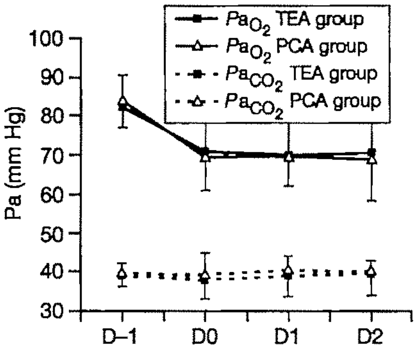

Fig 2 Arterial blood gases before and after surgery in both groups. Pa_{O_2}=arterial oxygen tension; Pa_{CO_2}=arterial carbon dioxide tension. D-1=preoperative day 1, D0=recovery room, D1=first postoperative day. Values are mean (SD).

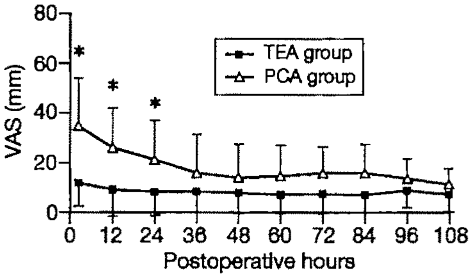

Fig 3 Evaluation of analgesia by VAS at rest. In the recovery room, two patients in the TEA group and seven patients in the PCA group were unable to score their pain on the VAS. Values are mean (SD). *$P<0.05$ between the two groups.

epidural group ($P<0.05$) after surgery. FVC values also fell by 63 and 55%, respectively ($P<0.05$) (Fig. 1). No differences were seen between groups. Arterial blood gas analysis also disclosed an approximately 15% decrease in Pa_{O_2}, similar and significant ($P<0.05$) for the two groups (Fig. 2).

The VAS was scored every 4 h at rest and while coughing. Figures 3 and 4 show the highest score recorded over the preceding 12 h for 4 days. At rest, the VAS score was lower the first day in TEA group and similar to i.v. PCA on the next day. Likewise, TEA provided better analgesia while coughing for the 4 days compared with PCA. In the i.v. PCA group, total amount of morphine given was 55 (SD 15) mg during the first 24 h and 147 (26) mg for 4 days. Mean rate of ropivacaine–sufentanil mixture given was 7.5 (1.4) ml h^{-1}. No side effect attributed to NSAIDs was noted.

On the first day, sedation scores were higher with i.v. PCA and episodes of arterial hypotension requiring boluses were more frequent with TEA (Table 3). Lowest recorded systolic arterial pressure was 77 (15) in the TEA group *vs* 115 (12) in the i.v. PCA group. There was no difference between the two groups with respect to other side effects during the 4 days of the study (Table 3). Three patients in each group developed mild temporal and spatial disorientation lasting 24 h. No cause was found including local anaesthetic toxiciy. During this period, the VAS score was not recorded and compliance with physiotherapy was unsatisfactory. In addition, the patients lost the ability to use the i.v. PCA pump. In the TEA group, no motor block (Bromage 2 or 3) was noted. One patient experienced paraesthesia of the upper limb, which resolved after withdrawal of the epidural catheter. No patient developed an infection at the puncture site but two patients (8%) had catheters colonized by coagulase negative staphylococci (greater than 200 c.f.u.). The length of hospitalization was 13.8 (3.9) (i.v. PCA group) *vs* 13.5 (4) days (TEA group) (P=0.12). Score of satisfaction for the two techniques of analgesia were: TEA 86 (12) and i.v. PCA 83 (15) cm (P=0.12).

Discussion

After thoracotomy, most postoperative deaths are the consequence of respiratory complications.[11 12] The incidence of these complications varies widely from one study to another (5–70%) because no clear definitions are presently available and clinical assessment may be subjective. CT scans provide an objective measure of the state of the lung resulting from the influence of analgesia on ventilatory mechanical dysfunction. Functional residual

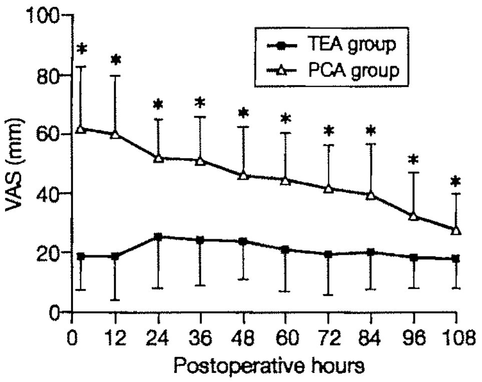

Fig 4 Evaluation of analgesia by VAS score during a cough. Values are mean (SD). *$P<0.05$ between the two groups

Table 3 Principal side effects with the two analgesic techniques. Values are expressed in percentage of patients. Arterial hypotension defined by value below 90 or 100 mm Hg if arterial hypertension history. *$P<0.05$

	PCA	TEA
Nausea-vomiting	23	20
Pruritus	4.5	4.5
Confusion	12	12
Sedation (S2) day 0	40 *	8
Sedation (S2) day 1, 2, 3	8	0
Arterial hypotension day 0	0	36*
Arterial hypotension day 1, 2, 3	0	8

capacity decreases sharply in the postoperative period, leading to the formation of collapsed lung tissue, beginning in the dependent regions. Active physiotherapy and pain control increase lung volume and may prevent consolidation.[13] Atelectasis is also thought to be an important cause of morbidity, leading to hypoxaemia, pneumonia and/or respiratory failure.[14 15] Diagnoses is generally based on daily chest x-rays. The incidence is 20–30%.[16] A comparison with data from CT scans shows that chest x-rays are rather insensitive, particularly for low position consolidation in the lower lung.[17] More than half of our patients presented with lung collapse (plate, segmental, and/or lobar atelectasis).

Peroperative atelectasis was virtually eliminated by performing re-expansion manoeuvres.[18] CT scans were obtained on the third day when the impact of analgesia was greatest. The scans were obtained after the inspiration of a normal tidal volume because the patients could not sustain a prolonged expiration. Radiological abnormalities seen earlier could have been influenced by the intraoperative period and pain was less intense up to day 3. We observed no atelectasis resulting from extrinsic compression, such as pleural effusion or gastric distention. This supports the idea that the reported incidence of these abnormalities reflects the quality of analgesia and postoperative physiotherapy.

Our main objective for analgesia was to obtain a VAS score at rest of less than 40 mm at rest at all times. Some authors have reported delays of 6–12 h before obtaining effective analgesia with i.v. PCA.[19] We attempted to avoid these delays by concentrating on early pain scores and giving rescue analgesia doses to either group to obtain efficient, prolonged pain control at rest. However, pain relief during coughing or deep breathing exercises could only be obtained with TEA and local anaesthetics, in agreement with previous studies.[4] A meta-analysis has also demonstrated that postoperative atelectasis is reduced by epidural analgesia.[20] However, the control patients were given nurse-controlled intermittent parenteral injections of opioids, which may have resulted in an inappropriate plasma opioid concentration. The absence of difference between our groups could be a result of two factors: first, better pain control provided by i.v. PCA, as plasma opioid concentrations remained within the therapeutic index;[21] second, the effect of multimodal analgesia, which reduces morphine consumption and improves the quality of analgesia.[22]

Respiratory physiotherapy designed to increase pulmonary volume prevents atelectasis and pulmonary complications.[23 24] Because all patients were informed preoperatively about the importance of physiotherapy to prevent respiratory complications, all of them, in the i.v. PCA group sustained 20-min physiotherapy sessions twice a day, despite their pain. In addition, deep breathing exercises were done with the same efficiency whatever the analgesic techniques used, as all the groups had comparable forced vital capacity values. Respiratory comfort during physiotherapy was better with TEA than with multimodal analgesia, but it had no beneficial effect on postoperative lung consolidation.

Our patients could be classified as low respiratory risk on the basis of preoperative pulmonary function tests. However, there is no data suggesting that spirometry can identify high risk patients because of its variable predictive value.[13] All the patients had been heavy smokers and almost half of them were smokers at the time of surgery; both of these factors are clinical respiratory risks.[25 26] Most of the patients in other studies had no clinical risk factors, which explains the lack of difference between systemic opioids and TEA in pulmonary complications.[5] Our population is representative of the large majority of patients undergoing thoracotomy, but it would be valuable to study the influence of TEA in a high risk groups selected with high risk factors.

We found no difference in clinical respiratory complications or in the length of hospital stays for the two groups of thoracotomized patients. The lack of statistical power to detect significant differences in true clinical outcomes could explain these results, as 150 patients would be required. Yeager and colleagues found an improvement in postoperative morbidity after thoracic surgery in high risk patients given epidural analgesia.[27] However, in the absence of preoperative respiratory characteristics, clear definitions and sensitive diagnosis assessment of atelectasis and clinical respiratory complications, it is difficult to affirm a clear benefit of central block on postoperative pulmonary morbidity compared with parenteral opioids in that study.

In summary, despite optimization of i.v. PCA, the administration of local anaesthetics and opioids delivered via a thoracic epidural catheter provides better analgesia while coughing. However, compared with multimodal analgesia and active physiotherapy, TEA does not improve spirometric or oxygenation parameters, nor the amount and size of atelectasis on a standard population of smokers undergoing resection of lung cancer.

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Efficacy and uptake of ropivacaine and bupivacaine after single intra-articular injection in the knee joint

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The efficacy of ropivacaine 100 mg (5 mg ml^{-1}), 150 mg (7.5 mg ml^{-1}) and 200 mg (10 mg ml^{-1}) and bupivacaine 100 mg (5 mg ml^{-1}) given by intra-articular injection into the knee after the end of surgery was studied in 72 ASA I–II patients scheduled for elective knee arthroscopy under general anaesthesia in a randomized, double-blind study. Kapake (paracetamol 1 g and codeine 60 mg) was given as a supplementary analgesic. Pain scores were assessed 1–4 h after surgery and a verbal rating scale of overall pain severity was assessed on second postoperative day. Ropivacaine or bupivacaine concentrations were determined in peripheral venous plasma up to 3 h after injection in eight patients in each group. Verbal rating pain scores were lower with ropivacaine 150 mg compared with bupivacaine 100 mg ($P<0.05$). There was a tendency for lower analgesic consumption and pain scores with all doses of ropivacaine (not significant). The mean (SD) maximum total plasma concentrations of ropivacaine were 0.64 (0.25), 0.78 (0.43), and 1.29 (0.46) mg litre^{-1} after 100, 150 and 200 mg. The corresponding unbound concentrations were 0.018 (0.009), 0.024 (0.020) and 0.047 (0.022) mg litre^{-1}. Both were proportional to the dose. The maximum total concentration after bupivacaine 100 mg was 0.57 (0.36) mg litre^{-1}. The time to reach maximum plasma concentration was similar for all doses and varied between 20 and 180 min. All concentrations were well below the threshold for systemic toxicity.

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The intra-articular administration of a local anaesthetic agent after arthroscopic surgery of the knee has been shown by the majority of studies to provide superior early postoperative analgesia compared with placebo,[1–5] though this has been called into question by several investigators.[6–8] A systematic review of 20 studies showed evidence for a reduction in postoperative pain after intra-articular local anaesthesia following arthroscopic knee surgery, which, although being slight to moderate and of short duration, may be of clinical significance in day-case surgery.[9] No adverse effects or toxicity attributable to the intra-articular administration of local anaesthetics were reported in this review. Synovial procedures have been reported to lead to increased absorption of bupivacaine as a result of the creation of extensive raw surfaces within the joint,[10] but a dose of bupivacaine 225 mg (7.5 mg ml^{-1}, 30 ml) was well tolerated. Peak concentrations have been reported to be minimized with shorter tourniquet inflation times and longer intervals between injection and tourniquet release.[11]

Ropivacaine is an aminoamide local anaesthetic with similar clinical efficacy to[12] and lower cardiotoxicity than racemic bupivacaine.[11 13] It is a long-acting local anaesthetic that is chemically homologous to bupivacaine and mepivacaine. Ropivacaine is in the form of the *S*-enantiomer, making it the first enantiomerically pure local anesthetic.[12] In contrast to bupivacaine, it has shown fewer inherent vasodilator properties after intradermal administration.[14] The purpose of this study was to compare the analgesic efficacy and systemic uptake of three different doses of ropivacaine administered as single intra-articular injections after arthroscopic knee surgery, with bupivacaine as a control.

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Methods

After local ethics committee approval and written informed consent, 72 ASA I or II patients scheduled for elective arthroscopy of the knee were recruited into the study. Patients were not recruited if they had a history of sensitivity to local anaesthetics or had received preoperative opioids or any other analgesics in the preceding 48 h. Patients with known osteoarthritis of the knee or the same discovered at surgery were excluded, as were those on whom synovial surgery was planned or had been performed. All patients were visited before surgery and instructed in the use of an Abbott Laboratory 10 cm visual analogue scale (VAS) for pain, with 0 cm as 'no pain' and 10 cm as 'worst pain imaginable'. A preoperative pain score on active flexion of the knee was recorded by the enrolling investigator.

Patients were unpremedicated and on arrival in the operating theatre all received a standardized general anaesthetic. This consisted of a sleep dose of propofol and alfentanil 10 μg kg^{-1}, after which a laryngeal mask was inserted. Anaesthesia was maintained using isoflurane (1–2%) with nitrous oxide (66%) in oxygen. Non-invasive monitoring was undertaken, consisting of ECG, arterial blood pressure, peripheral oxygen saturation, FE'_{CO_2} and FI_{O_2}.

Patients were allocated to one of four groups of 18 patients in a double-blind, randomized manner using randomly selected sealed envelopes. They received ropivacaine 100 mg (5 mg ml^{-1}, group R100), ropivacaine 150 mg (7.5 mg ml^{-1}, group R150), ropivacaine 200 mg (10 mg ml^{-1}, group R200) or bupivacaine 100 mg (5 mg ml^{-1}, group B100) in a 20 ml intra-articular injection at the end of surgery. A syringe of the corresponding local anaesthetic was prepared by an assistant who took no further part in the study. The anaesthetist, surgeon, observer and patient were all unaware of the nature of the contents of each syringe. These drugs were administered by intra-articular injection by the surgeon on completion of surgery, 5 min before deflation of the tourniquet, which had been inflated to a pressure of 300 mm Hg. All patients had 2% lidocaine 2 ml with epinephrine infiltrated into each skin wound at the end of surgery. In eight patients in each group, blood (5 ml) was drawn from a dedicated, unheparinized cannula sited in the non-injection antecubital fossa before (time 0) and 10, 20, 30, 45, 60, 90, 120 and 180 min after completion of the local anaesthetic injection. These samples were centrifuged as soon as possible after collection and the separated plasma was frozen at −80°C until assay. The total plasma concentrations of ropivacaine and bupivacaine base were determined by high-performance liquid chromatography with ultraviolet detection at 210 nm using bupivacaine as the internal standard. The limit of quantitation of the method was 50 ng ml^{-1}. The unbound (free) plasma concentration of ropivacaine base was determined by coupled column liquid chromatography with ultraviolet detection at 210 nm after ultrafiltration of the plasma samples.[15] The limit of quantitation was 3 ng ml^{-1}. The unbound concentration was determined in peak plasma samples of ropivacaine or in samples taken at an adjacent sampling time.

Postoperative pain scores (VAS, 0–100 mm) on active flexion of the knee were recorded by a blinded observer 1, 2 and 4 h after the intra-articular injection. Postoperative pain was treated by the ward nursing staff with paracetamol 1 g + codeine phosphate 60 mg (Kapake) and, if this did not provide adequate analgesia, as judged by recovery nursing staff, morphine 0.15 mg kg^{-1} was administered i.v. Patients were discharged 4 h after surgery if comfortable, with analgesic packs and instructions to take the above dose of Kapake up to every 4 h if needed. The time to the first request for analgesia and the total analgesic requirements were recorded. Patients were telephoned at home on the second postoperative day and their post-discharge analgesic use and a subjective verbal rating of overall pain severity were recorded. Ratings were 'no pain', 'mild pain', 'moderate pain' and 'severe pain' and were identified as such for reference purposes on the record chart given to the patient on discharge from hospital.

Physical characteristics, operation type and duration were analysed by analysis of variance (ANOVA) and the χ^2 test when appropriate, and their relationships to pain scores tested with Spearman's rank correlation. Pain scores were analysed by ANOVA and time to first analgesia by survival analysis. Analgesic tablet consumption and verbal rating scale scores were analysed with the Mann–Whitney *U*-test. Results were considered statistically significant when $P<0.05$. To achieve an 80% power of detecting a 15 mm difference in VAS score, the study required 18 patients in each group if the common standard deviation of pain scores in all groups is 5 mm.

The total (C_{max}) and unbound ($C_{u,max}$) peak plasma concentrations were estimated from the observed values. The area under the plasma concentration-time curve during the 3 h of observation (AUC_{0-3}) was calculated using the trapezoidal rule. The fraction of unbound drug in plasma (f_u) was calculated as the unbound divided by the total plasma concentration. Dose proportionality for C_{max}, $C_{u,max}$ and AUC_{0-3} were analysed with the power model $y=\alpha dose\beta$, where α depends on subject, period and error.[16] This model assumes a linear relationship between log y and log dose. Dose proportionality requires that $\beta=1$ for dose-dependent parameters. In terms of this model, a doubling of the dose is reflected in the ratio $R=2\beta$ of corresponding effects, i.e. $(y_2/y_1)=2\beta$. If dose proportionality holds, the effect ratio R equals 2. A simple linear regression was also used to study the relationships of dose with C_{max}, $C_{u,max}$ and AUC_{0-3}. Ninety per cent confidence intervals for the intercepts were calculated.

Results

Patient characteristics were similar in all groups. Neither the nature of the procedure (whether diagnostic or therapeutic)

Table 1 Patient characteristics, type of surgery and tourniquet time in the groups receiving ropivacaine 100 mg (R100), ropivacaine 150 mg (R150), ropivacaine 200 mg (R200) and bupivacaine 100 mg (B100). Mean (SD) or number of patients

	Group			
	R100 (*n*=18)	**R150 (*n*=18)**	**R200 (*n*=18)**	**B100 (*n*=18)**
Age (yr)	33 (12.1)	36 (9.9)	33 (9.4)	34 (7.7)
Weight (kg)	82 (14.5)	85 (15.8)	83 (11.8)	84 (9.3)
Height (cm)	172 (15.1)	176 (12.0)	172 (8.8)	175 (15)
Sex (M/F)	16/2	14/4	17/1	17/1
Type of surgery (diagnostic/therapeutic)	5/13	6/12	3/15	3/15
Tourniquet time (min)	27.9 (7.6)	27.2 (6.5)	28.1 (8.7)	26.7 (4.9)

Table 2 Median analgesic consumption (number of tablets per patient) and mean (SD) time to first request of analgesia in the groups receiving ropivacaine 100 mg (R100), ropivacaine 150 mg (R150), ropivacaine 200 mg (R200) and bupivacaine 100 mg (B100)

	Group			
	R100 (*n*=18)	**R150 (*n*=18)**	**R200 (*n*=18)**	**B100 (*n*=18)**
No. of analgesics 0–24 h	2	2	2	3
No. of analgesics 24–48 h	0	0	0	2
No. of patients requiring no analgesics	4	7	3	2
Time to first analgesia (min)	1002 (1070)	1383 (1269)	938 (953)	719 (703)

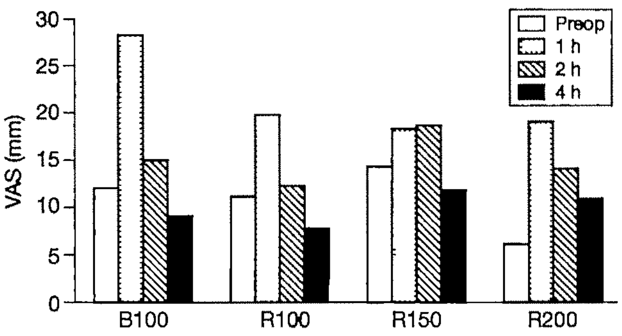

Fig 1 Median pain scores (VAS, mm) before surgery and 1, 2 and 4 h after surgery in the groups receiving ropivacaine 100 mg (R100), ropivacaine 150 mg (R150), ropivacaine 200 mg (R200) and bupivacaine 100 mg (B100).

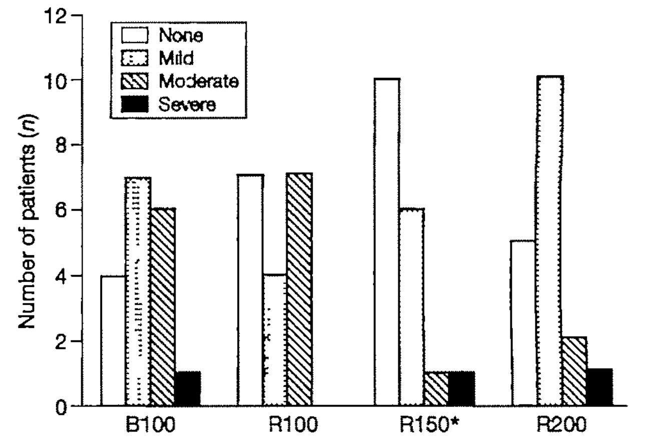

Fig 2 Patients' verbal pain rating scale (none, mild, moderate or severe) on the second postoperative day in the groups receiving ropivacaine 100 mg (R100), ropivacaine 150 mg (R150), ropivacaine 200 mg (R200) and bupivacaine 100 mg (B100). *$P<0.05$ R150 *vs* B100.

nor the duration of tourniquet inflation were different between the groups (Table 1). All 72 patients completed the study. The median postoperative pain score varied between 6 and 28 mm, and there were no statistically significant differences between the groups in pre- and postoperative pain scores or in the postoperative change from preoperative pain scores (Fig. 1). The median analgesic consumption in the first and second postoperative 24 h periods were lower in all three ropivacaine groups than in the bupivacaine group; these differences did not achieve statistical significance (Table 2). Both the number of patients who did not consume postoperative analgesics and the time to first analgesic consumption tended to be highest in group R150, but there was no statistically significant difference. The median verbal rating scale scores of the overall pain experienced by the patient were significantly lower ($P<0.05$) in group R150 (Fig. 2). One patient only, in group R150, required the administration of morphine for breakthrough pain. Increased pain scores at 1 h were correlated with an increased tourniquet time ($P<0.05$) and with preoperative pain scores ($P<0.01$). Preoperative and postoperative pain scores were strongly and positively related to analgesic consumption and negatively to the time to first analgesic request ($P<0.001$).

The total plasma concentration–time curves over the 3 h after local anaesthetic administration for each patient in all groups are shown in Fig. 3. The highest individual peak plasma concentration measured was in group R200 (2.2 mg litre^{-1} at 30 min) and was associated with an

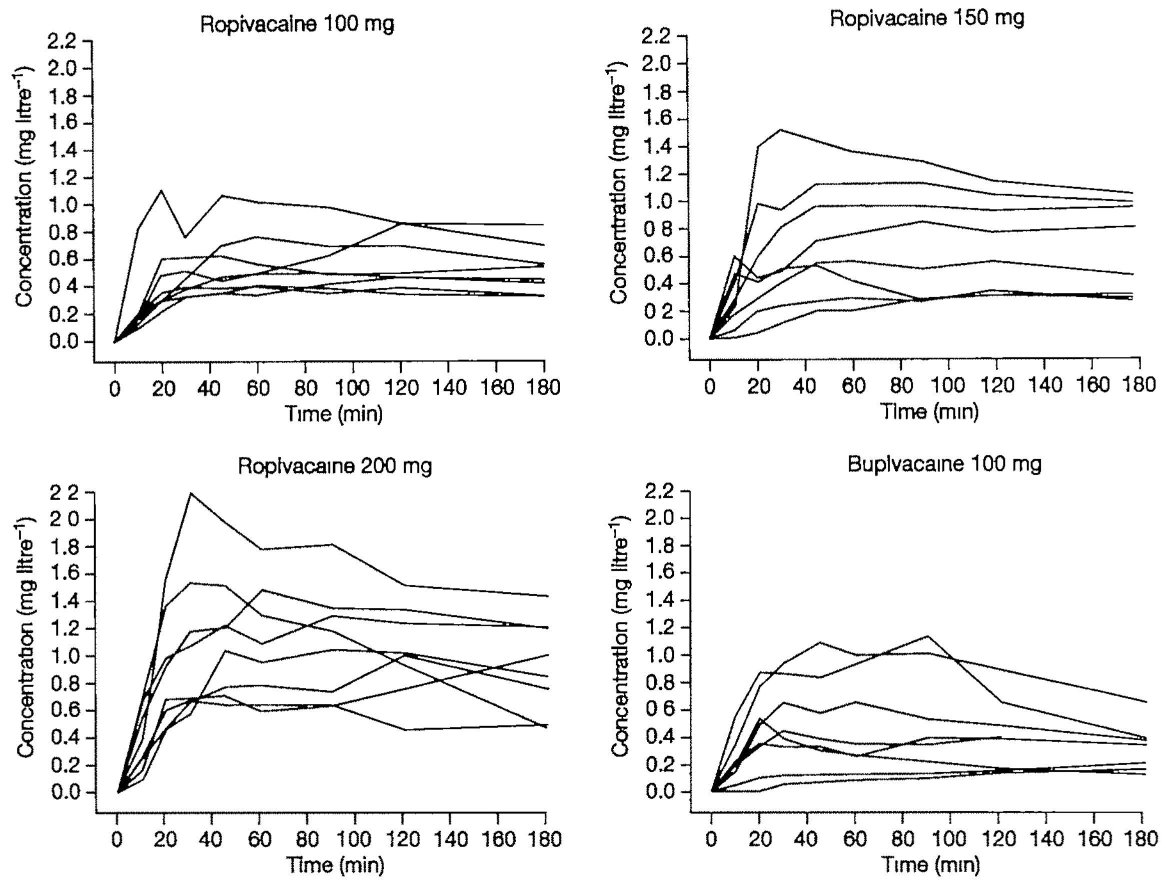

Fig 3 Individual total plasma concentrations after single intra-articular injection of ropivacaine 100, 150 and 200 mg and bupivacaine 100 mg in patients scheduled for elective arthroscopy of the knee (*n*=8 in each group)

Table 3 Mean (SD) pharmacokinetic parameters after single intra-articular injections of ropivacaine 100, 150 and 200 mg and bupivacaine 100 mg in patients scheduled for elective arthroscopy of the knee. *Median (minimum/maximum); †*n*=7. AAG, α_1-acid glycoprotein

	Group			
	R100 (*n*=8)	**R150 (*n*=8)**	**R200 (*n*=8)**	**B100 (*n*=8)**
t_{max} (min)*	60 (20/180)	75 (30/180)	75 (30/180)	53 (20/180)
C_{max} (mg litre^{-1})	0.64 (0.25)	0.78 (0.43)	1.29 (0.46)	0.57 (0.36)
AUC_{180} (mg min litre^{-1})	91 (32)	114 (64)	170 (66)	68 (50)
f_u at C_{max} (%)	2.8 (0.9)	2.8 (1.2)	3.5 (1.1)	
$C_{u,max}$ (mg litre^{-1})	0.018 (0.009)	0.024 (0.020)	0.047 (0.022)	
AAG (µmol litre^{-1})	18.2 (4.1)†	17.9 (2.0)†	19.1 (3.2)	

unbound concentration of 0.061 mg litre^{-1}. Time to C_{max} (t_{max}) was similar for all doses and occurred at the last sampling time in one patient in each ropivacaine group and in two patients in the bupivacaine group, indicating slow uptake. Mean C_{max} and t_{max} were similar after R100 and B100 (Table 3). In common with all study patients, neither of these patients showed any sign of systemic local anaesthetic toxicity.

C_{max} (Fig. 4), $C_{u,max}$ (Fig. 5) and AUC_{0-3} (Fig. 6) were proportional to the dose after intra-articular administration of ropivacaine, as the intercepts of the linear regression lines were close to zero. The 90% confidence limits for the intercepts were −0.59 and 0.46 for C_{max}, −0.037 and 0.010 for $C_{u,max}$ and −1.12 and 1.35 for AUC_{0-3}. The point estimates for C_{max}, $C_{u,max}$ and AUC_{0-3} in the power model further support dose proportionality, with a point estimate of β close to 1 and an *R* value close to 2 (Table 4). Based on the *R* values, the increase in C_{max}, $C_{u,max}$ and AUC_{0-3} with a doubling of the dose was 96, 143 and 78% respectively. The mean (SD) f_u estimated at C_{max} was 3.1 (1.1)%. The concentration of α_1-acid glycoprotein was similar between the ropivacaine groups and was in the normal range.

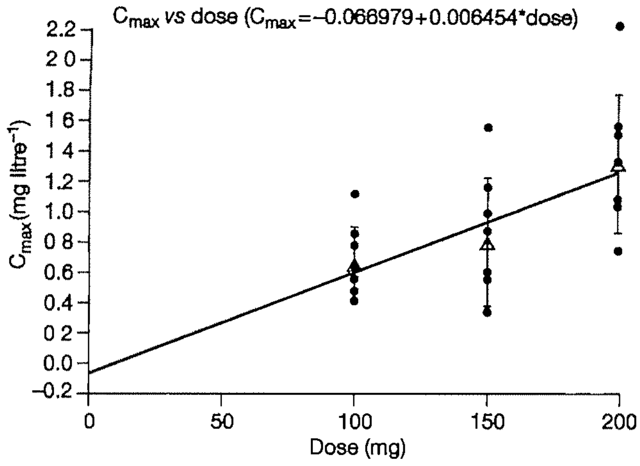

Fig 4 Mean (SD) and individual total C_{max} in plasma *vs* dose, with a fitted linear regression line, after single intra-articular injection of ropivacaine 100, 150 and 200 mg in patients scheduled for elective arthroscopy of the knee (n=8 in each group).

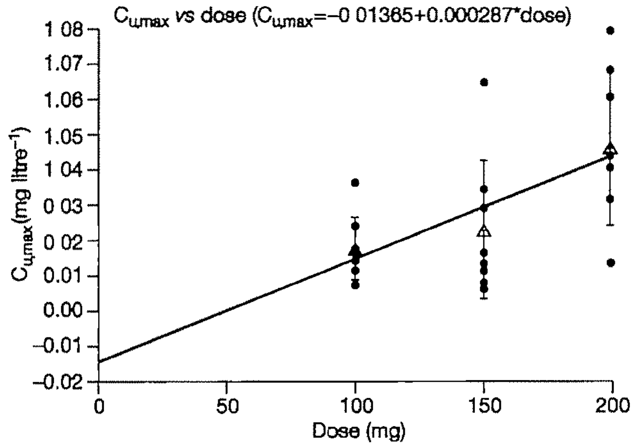

Fig 5 Mean (SD) and individual total $C_{u,max}$ in plasma vs dose, with a fitted linear regression line, after single intra-articular injection of ropivacaine 100, 150 and 200 mg in patients scheduled for elective arthroscopy of the knee (n=8 in each group).

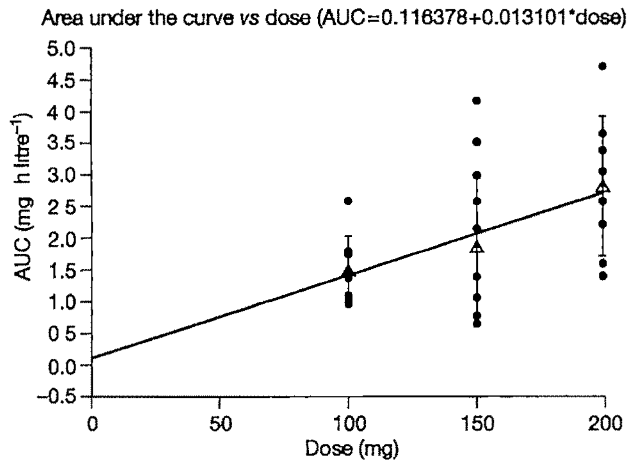

Fig 6 Mean (SD) and individual total AUC0–3 in plasma *vs* dose, with a fitted linear regression line, after single intra-articular injection of ropivacaine 100, 150 and 200 mg in patients scheduled for elective arthroscopy of the knee (n=8 in each group).

Discussion

Intra-articular long-acting local anaesthetics are the standard for post-arthroscopy analgesia in our institution. Our experience is supported by a recent review of 20 studies based on 900 patients for whom there is evidence of a definite reduction in postoperative pain associated with the use of intra-articular local anaesthetics, suggesting a clinical benefit in day-case surgery.[9] More studies detected differences in analgesic consumption than in pain scores. Previous authors have suggested that post arthroscopy discomfort is a poor model of pain because a high percentage of patients had minimal pain scores and required no supplementary analgesics.[17] Our finding that 78% of patients took postoperative analgesics is consistent with a previous study.[18] The relationship observed between postoperative pain scores and analgesic consumption in the present study suggests variable rather than insignificant postoperative pain.

In this study pain scores demonstrated similar variability to that in work reported previously.[19] As a result, there were non-significant consistent differences between groups in VAS pain scores in the first 4 h after surgery and in analgesic consumption in the first 48 h after surgery. However, for the verbal rating pain score, a significant improvement was seen with ropivacaine 150 mg compared with bupivacaine. In ethical clinical trials, pain scores should tend towards convergence with the free availability of analgesics, and serve to emphasize the adequacy of the rescue analgesic in placebo or control groups. In situations such as this, it may well be that analgesic consumption and overall patient satisfaction would be more reliable and appropriate measures than pain scores.

All patients had their skin entry wounds (two or three wounds) injected with a uniform dose of lidocaine and epinephrine in an attempt to standardize the effect of postoperative pain from these sites for at least the early VAS pain scores. This may have had the effect of removing a large component of the early postoperative pain, perhaps reducing early differences between the groups. Postoperative pain may have been further reduced across all groups by the interval of 5 min between injection and tourniquet deflation and the consequent increase in tissue uptake of the local anaesthetics.[11] Furthermore, ropivacaine has anti-inflammatory effects in human mucosal cells,[20] which may contribute to the observed difference in analgesic effect on the second postoperative day.

The systemic uptake of the two local anaesthetics from the knee joint appears similar, as reflected by their corresponding C_{max} and t_{max} values. The similarity of these times in this study suggests that there was little difference in the vasomotor activities of the agents at the studied doses at this site. C_{max} was considerably higher than previously described for intra-articular bupivacaine, probably as a result of the extended tourniquet inflation time and the hyperaemia resulting from post-ischaemic reperfu-

Table 4 Results of power model analysis in the evaluation of dose proportionality based on single intra-articular injections of ropivacaine 100, 150 and 200 mg in patients scheduled for elective arthroscopy of the knee (n=8 in each group)

Pharmacokinetic variable	n	β			R		
		Point estimate	90% confidence limits		Point estimate	90% confidence limits	
			Lower	Upper		Lower	Upper
AUC_{0-3}	24	0.83	0.24	1.42	1.78	1.18	2.67
C_{max}	24	0.97	0.40	1.54	1.96	1.32	2.90
$C_{u,max}$	24	1.28	0.50	2.06	2.43	1.41	4.18

sion.[11] Plasma drug concentrations were still slowly rising in five patients (two receiving bupivacaine and three receiving ropivacaine) in the 180 min sample, although the curves were similarly shaped across the groups. The sustained plasma drug concentrations observed over the sampling period may be consistent with prolonged absorption exceeding the true elimination rate (i.e. the absorbtion/elimination rate that would be seen after i.v. administration of ropivacaine or bupivacaine, which have terminal half-lives of 1.9 and 2.7 h respectively).[21] This may be at least partially technique-specific in this case, because of the delay between injection and tourniquet deflation and the fact that the uptake of both drugs was considerably slower than reported previously for bupivacaine.[11] Prolonged uptake of drug from the joint might also reasonably be expected to extend the analgesic effect. Limitation of elimination by the absorption rate has been reported for ropivacaine after epidural administration.[22] Prolonged systemic absorption has also been described after infiltration of the hernia wound with ropivacaine, the plasma concentration being elevated for the entire 2 h sampling period.[23]

In this study, the peak concentrations of both total and unbound ropivacaine were proportional to the dose administered, which is important in allowing predictability in analgesia and in the risk of systemic effects in clinical practice. Intersubject variability, however, is the largest unpredictable factor in this regard, and our curves appear to confirm this. Nevertheless, all total and unbound individual peak plasma concentrations for each drug and dose were well below the recognized toxic threshold.[13] Bupivacaine administered intra-articularly to the knee has been associated with cardiovascular toxicity despite the use of accepted doses.[24] This was probably as a result of an accidental intravascular injection in this relatively vascular joint, and in such a situation the lower cardiotoxicity of ropivacaine[12] [13]would be beneficial.

In conclusion, we have demonstrated that ropivacaine and bupivacaine 100 mg provide similar and effective post-arthroscopy analgesia and that ropivacaine at the higher dose of 150 mg appears to further reduce patients' pain ratings in the 48 h period after surgery. A higher ropivacaine dose does not seem to improve efficacy. Plasma concentrations for all patients and all doses fell below the estimated toxic thresholds, and therefore it seems that these drugs can be safely administered by intra-articular injection.

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Effect of peri- and postoperative epidural anaesthesia on pain and gastrointestinal function after abdominal hysterectomy

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In a double blind study we have investigated the effects of epidural local anaesthesia (LA), when added to general anaesthesia (GA) and postoperative paracetamol and NSAID, on postoperative pain and gastrointestinal function in patients undergoing open hysterectomy. Sixty patients were randomized into three study groups: GA, and postoperative paracetamol and NSAID (GA, n=20); GA, paracetamol, NSAID, intraoperative epidural lidocaine and 24-h postoperative epidural saline (Saline, n=20); or GA, paracetamol, NSAID, intraoperative epidural lidocaine and 24-h postoperative epidural bupivacaine (Bupi, n=20). Patients were observed for 72 h postoperatively. Pain at rest, during cough, and mobilization, request for supplementary morphine, and time to first postoperative flatus, was reduced in patients receiving 24-h postoperative epidural anaesthesia, compared with the two other groups. However, these effects of epidural LA, were not sustained beyond the period of infusion, and no differences in PONV, time to first postoperative defecation, mobilization or time to discharge from hospital were observed between groups. A 24 h postoperative epidural infusion with bupivacaine, when added to postoperative paracetamol and NSAID, reduces pain and opioid requirements, but has only limited effects on gastrointestinal function and patient recovery.

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Abdominal hysterectomy is associated with moderate to severe postoperative pain,[1–3] significant nausea and vomiting[4–7] and reduced gastrointestinal (GI) motility. Reduced GI motility is considered to be a result of nociceptive and sympathetic neural activity induced by surgery, and may last for 2–5 days, depending on the technique applied for anaesthesia and postoperative analgesia.[7–10]

Epidural local anaesthetics (LA) results in effective pain relief[11] and improved GI motility compared with opioid-based analgesia after hysterectomy.[8 7 12] However, relative importance of spinal reflex activity induced by surgery/postoperative pain, and perioperative opioid administration, for the reduction in GI motility, is not settled.[13] Hence, the beneficial effect of epidural LA on postoperative GI function may be a result of neural block during and/or after surgery reduced opioid consumption, or both.

Paracetamol and NSAIDs have been shown to reduce pain and the need for opioids after hysterectomy.[14 15] In a recent study, combined paracetamol, NSAID, and continuous 24 h infusion of epidural LA provided effective postoperative pain relief after hysterectomy. Median time to first passage of flatus and faeces was less than 48 h. It was not clear from this study, however, whether the relatively short duration of GI paralysis was because of administration of intra- and postoperative epidural LA, an opioid-sparing effect of paracetamol and NSAID, or both.[11]

The aim of this study was to compare the effect of combined general anaesthesia and postoperative paracetamol and NSAID, with or without intraoperative, or intra- and 24 h postoperative epidural LA, on pain and GI function after abdominal hysterectomy.

Patients and methods

Sixty patients aged 18–75 yr undergoing elective abdominal total or supravaginal hysterectomy through a Phannenstiel or inferior median incision were included in the study. Informed written consent was obtained from all patients and approval was obtained from the

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Table 1 Patient and perioperative data (median (range) or number)

	Group		
	GA group	**Saline group**	**Bupi group**
No of patients	20	20	20
Age (yr)	54 (40–75)	49.5 (32–70)	50.5 (41–75)
Weight (kg)	68(50–90)	73 (50–95)	70 (54–90)
Height (cm)	167(160–175)	165 (150–176)	164(153–180)
Phannenstiel/inferior median incision	15/5	14/6	17/3
Duration of surgery (min)	88 (47–151)	81 (55–141)	75 (59–110)
Perioperative propofol (mg)	1285 (782–2123)	1075 (607–2270)	1185 (769–1629)
Perioperative fentanyl (mg)	0.5 (0.3–0.9)	0 (0–0)	0 (0–0)
Perioperative haemorrhage (ml)	275 (50–1600)	200 (100–1200)	200 (20–1000)
Perioperative sodium chloride (ml)	1350 (800–2400)	1200 (500–2500)	1200(1000–2200)
Perioperative 6% HAES (ml)	500 (0–1000)	500 (0–1000)	500 (0–1000)
Perioperative ephedrine (mg)	0 (0–0)	5 (0–25)	2.5 (0–60)

local Ethics Committee and the Danish National Board of Health. Patients were recruited from the Department of Gynaecology, Herlev University Hospital, during the period January 1999 to September 2000. Patients were not included if they were unable to cooperate, had a body weight ⩾ (1.3×body height (cm) − 100), moderate to severe heart or lung disease (ASA ⩾III), a history of drug or alcohol abuse, chronic pain or daily intake of analgesics, or had contraindications to NSAIDs or to insertion of an epidural catheter.

Preoperatively, patients were randomized by a computer program to general anaesthesia (the GA group), or combined general and epidural anaesthesia, using sealed envelopes. For patients randomized to combined general and epidural anaesthesia, a number referring to the postoperative epidural study drug, was stated in the envelope.

One hour before surgery patients had sublingual triazolam 0.125 mg.

Patients randomized to GA were induced with propofol 1.5–2.5 mg kg^{-1}, alfentanil 1.0 mg, fentanyl 0.3 mg, and rocuronium 0.6 mg kg^{-1}, and a tracheal tube was inserted. Propofol was given without nitrous oxide for maintenance of anaesthesia. If arterial pressure and/or heart rate increased to greater than 120% of initial values, fentanyl 0.1 mg was administered.

Patients randomized to epidural treatment, had an 18-gauge epidural catheter inserted through a Touhy needle and advanced 4–5 cm into the epidural space at the T10–11 level, and a 4 ml test dose of 2% lidocaine with ephinephrine was administered. A bolus dose of 16 ml of 2% lidocaine with epinephrine was administered, followed by continuous infusion of 8 ml h^{-1} of 2% lidocaine throughout the operation. General anaesthesia was induced with propofol 1.5–2.5 mg kg^{-1} and alfentanil 1.0 mg, and a laryngeal mask airway (LMA[†]) was inserted. Propofol without nitrous oxide was given for maintenance of anaesthesia. No additional doses of lidocaine or alfentanil were given.

For all patients, hypotension was treated with i.v. infusion of isotonic sodium chloride, HAES 6% or ephedrine 5 mg i.v. in incremental doses, when systolic arterial pressure was below 90 mm Hg. Fluid and blood losses were replaced according to the prescriptions of the department.

At skin closure, patients in the epidural group received bupivacaine 0.2% (the Bupi group) or saline (the Saline group) as a bolus of 8 ml and continuous infusion of 8 ml h^{-1} for 24 h. The study drugs were prepared by the hospital pharmacy in identical containers, marked with a number, the name of the project and the investigators name. This part of the study was double blinded.

For the first 48 h after surgery, all patients received 2 G paracetamol rectally every 8 h, thereafter 1 G orally every 6 h. For the first 72 h, all patients received ketorolac 30 mg i.m. every 8 h. If additional analgesic was required, morphine 0.125 mg kg^{-1} was given.

Patients were given ondansetron 4 mg i.v., if they demanded antiemetics. If an additional antiemetic was required before another dose of ondansetron could be administered (8 h), metoclopramide 10 mg i.v. was given.

All patients were instructed preoperatively on the use of the visual analogue scale (VAS) pain score, and to request supplementary analgesic and antiemetics if needed.

Pain scores were assessed by the patients at 4, 6, 22, 24, 26, 30, 48, and 72 h after the operation on a VAS (0 mm=no pain, 100=worst pain imaginable) at rest, on coughing, and on mobilization from the supine to the sitting position. The number of morphine doses was recorded at the same times. Levels of sensory block to pinprick were assessed bilaterally at 6, 24, 26, and 30 h after operation; in the event of asymmetrical block the most extensive spread was recorded. Motor block was assessed using a four-point modified Bromage scale (0=no motor block, 1=inability to raise extended legs, 2=inability to flex knees, 3=inability to flex ankle joints) at 6, 22, 24, 26, and 30 h after operation. Ability to walk on the floor (0=no difficulty, 1=little difficulty, 2=very difficult, 3=impossible, 4=difficult or impossible for other reasons than motor block) was assessed

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[†] LMA is the property of Intavent Limited

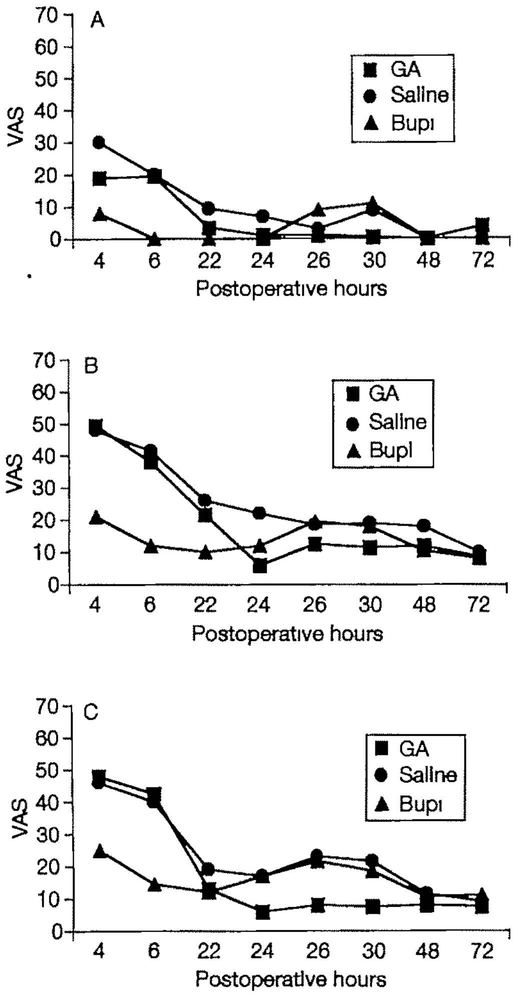

Fig 1 Median visual analogue scale (VAS) pain scores (A) at rest, (B) during coughing, and (C) during mobilization from the supine to the sitting position. VAS pain scores were significant lower both at rest, during cough and during mobilization until 24 h after the operation in the Bupi group, compared with both the GA group and the Saline group.

at 6, 22, 24, 26, 30, and 48 h after operation. The actual duration of mobilization (<1, 1–4, or >4 h) during the 24–48 and 48–72 h intervals was assessed at 48 and 72 h after the operation. Patients who were not able to mobilize at >4 h were asked for the primary reason for this. At all visits, gastrointestinal function was monitored by asking the patients if and when they had first passage of flatus and faeces, and if they had experienced nausea (0=no, 1=light, 2=moderate, 3=severe) and/or vomiting since last assessment.

Patients were encouraged to eat and drink whenever possible after the operation. Ingestion of predefined quantities of food and beverages was assessed at 24, 48, and 72 h after the operation.

Every 24 h after the operation, patients were assessed as ready or not ready for discharge from hospital, by four discharge criteria: (1) Normal defecation and no urinary retention: yes/no; (2) able to mobilize and dress: yes/no; (3) need for opioid: yes/no; (4) surgical complication requiring patient hospitalized: yes/no. When the patient scored yes on the two former, and no on the two latter questions, they were assessed ready for discharge from hospital.

The primary end-points of this study were pain during coughing, and time to first passage of faeces. Power calculation for the pain score was based on results from an unpublished pilot study performed at our institution (VAS pain scores during cough, in the general anaesthesia group, 24 h after the operation: 40 mm; type 1 error: 5%, type 2 error: 20%; minimal difference not to be overlooked: 20 mm reduced pain score; sample size needed: 16 patients in each group). Power calculation for time to first postoperative defecation was also based on the results from the unpublished pilot study in hysterectomy patients. (On day 3 after the operation, 17% have defaecated. Other type 1 error: 5%; type 2 error: 20%; minimal difference not to be overlooked: 50% reduction in time to first postoperative defecation: sample size needed 14 patients in each study group.) Data are presented as medians with upper and lower quartiles. Statistical analyses were performed using the Mann–Whitney rank sum test for unpaired data, Wilcoxon signed rank sum test for paired data, and Fisher's exact test for dichotomous data, where appropriate If multiple testing was performed, significant *P* values were corrected with a Bonferroni factor for multiple comparisons.

In addition, a longitudinal analysis of VAS pain scores was performed. In order to make the normality assumption more reasonable, we performed a square root transformation of the VAS scores before analysis. The model allowed for correlation between measurements on the same patient, in the form of a random level and an autoregressive error over time. Apart from 'time itself' (regarded as a categorical variable to allow for maximal flexibility) and treatment group, we considered the covariates 'duration of operation', 'age of patient' and 'Phannenstiel or median inferior incision'. The analyses were made for three different VAS pain scores: at rest, during cough and during mobilization, and each 24 h interval was treated separately. A Cox regression analysis with time to first postoperative faeces and flatus as dependent variables was performed. Covariates chosen beforehand were: treatment group, duration of operation, milligram of morphine before the event and age. *P*<0.05 was considered statistically significant Calculations were performed using SPSS 9.0 for Windows and SAS 6.12 (PROC MIXED procedure).

Results

We considered 173 patients for inclusion in the study. One hundred and six patients were not included: 10 were aged more than 75 yr; four were unable to communicate properly, 13 were adipose; six had moderate to severe heart or lung disease or disseminated cancer; 10 used analgesics or

Table 2 Number of patients who requested morphine, and number of doses administered. ns=not significant

Postoperative period	Group			*P*
	GA group	Saline group	Bupi group	
0–24 h				
No of patients receiving morphine	19/20	20/20	14/20	0.02
No of doses in patients receiving morphine	87	124	35	0.001
24–48 h				
No of patients receiving morphine	7/20	6/20	9/20	ns
No of doses in patients receiving morphine	12	11	11	ns
48–72 h				
No of patients receiving morphine	4/20	5/20	3/20	ns
No of doses in patients receiving morphine	10	7	8	ns

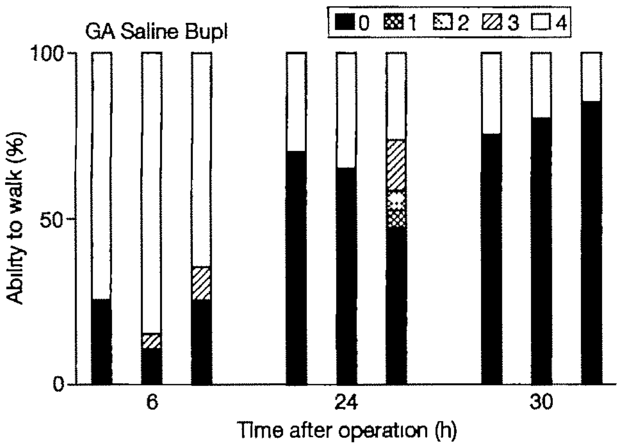

Fig 2 Motor function, assessed by walking on the floor: 0=no difficulty; 1=little difficulty, 2=very difficult; 3=impossible; 4=difficult or impossible for other reasons than motor block. Columns show percentages of patients with a particular score in the GA-, the Saline- and the Bupi groups at 6, 24, and 30 h after the operation. No significant differences between groups

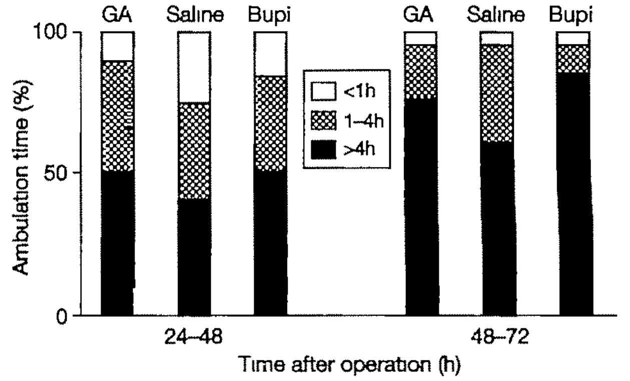

Fig 3 Patient assessed actual duration of mobilization. <1, 1–4, and >4 h. Columns show percentages of patients with a particular score in the GA-, the Saline- and the Bupi groups at the 24–48 and 48–72 h intervals. No significant differences between groups.

suffered alcohol abuse; three had other surgical procedures in addition to hysterectomy; two needed anaesthetic procedures other than allowed in the protocol; 11 had contraindications to NSAIDs; 43 did not want to participate either because they wanted (n=13) or did not want (n=30) insertion of an epidural catheter; and four patients were not included because of lack of time. Sixty patients were included in the study, but seven of these were excluded: five after randomization but before operation (two because of withdrawal of consent after randomization to epidural catheter, two because it was not possible to insert an epidural catheter and one because of change in the surgical procedure); and two at 8 h (one because of haemorrhage and reoperation and one because of withdrawal of consent). The hospital pharmacy produced a new series of sealed envelopes and blinded medicine in replacement for the seven excluded patients, and seven new patients were included. Thus data from 60 patients were included and analysed.

There were no significant differences between groups for patient characteristics or operative data, except for per-operative fentanyl and ephedrine (Table 1). Eleven and 10 patients in groups 2 and 3, respectively, needed i.v. ephedrine.

VAS pain scores were significantly lower both at rest (P=0.006), during cough (P=0.01), and during mobilization (P=0.01) until 24 h after the operation in the Bupi group, compared with both the GA group and the Saline group (Fig. 1A–C). Following the first 24 h after the operation there were no significant differences. Neither the duration of operation, age of patient, nor type of incision had significant influence on pain scores according to the longitudinal analysis.

Patients in the Bupi group requested a significantly smaller amount of supplementary morphine from 0–24 h compared with the other two groups. There were no significant differences in the number of patients requesting supplementary morphine, or in the number of doses, between groups at 24–48 or 48–72 h after the operation (Table 2).

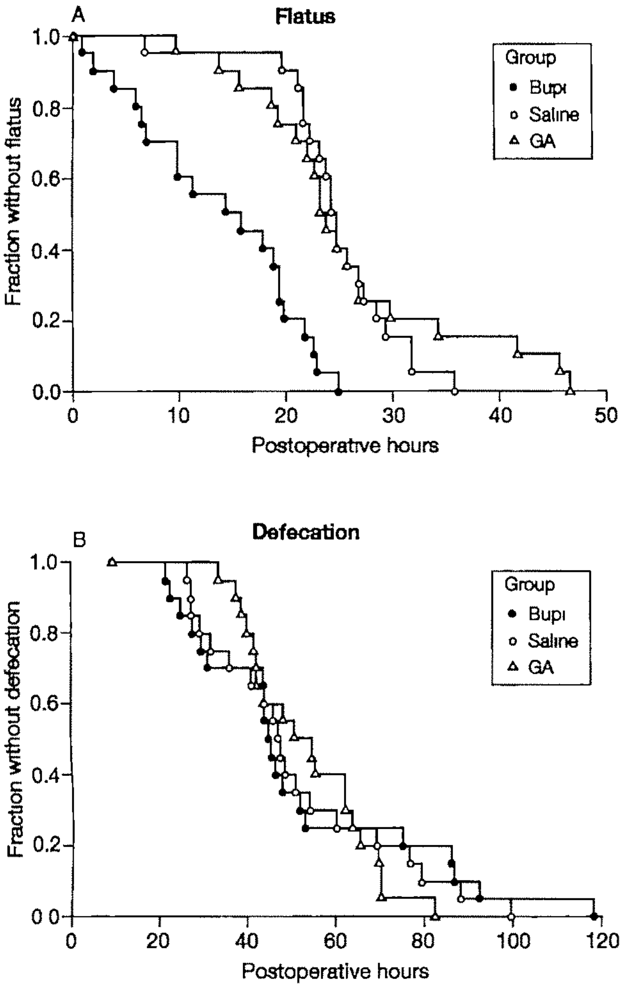

Fig 4 Fraction of patients without flatus (A) and defecation (B) in the postoperative period. Time to first postoperative passage of flatus was significantly reduced in the Bupi group compared with the other two groups (P=0.009) whereas time to first postoperative defecation was not different between groups (P=0.70)

Preoperatively patients receiving epidural treatment had a sensory block extending from at least Th6 to L3 (median 13 dermatomes). Preoperatively and at 4 h after the operation, there were no significant differences in the spread of sensory block between the Saline and the Bupi group. At 6, 22, 24, and 26 h after the operation, patients in the Saline group had a smaller spread than those in the Bupi group (P<0.035, after Bonferroni correction for seven comparisons).

There were no significant differences in motor block, assessed by the modified Bromage scale, at any assessment. At 24 h after the operation, 70% in the GA group compared with 65% in the Saline group and 45% in the Bupi group were able to walk on the floor without difficulty (P>0.05); at 30 h the corresponding numbers were 75, 80, and 85% (P>0.05) (Fig. 2). At 24 h after the operation, the ability to walk could not be evaluated for different reasons. In the GA group, patients stated dizziness (15%) and nausea (15%) as primary reasons, in the Saline group pain (20%) and nausea (10%), and in the Bupi group motor block (20%) and dizziness (20%). There were no differences in the actual duration of mobilization (Fig. 3). The primary reasons for mobilizing <4 h were pain and fatigue both in the 24–48 and 48–72 h intervals.

Time to first postoperative passage of flatus was significantly reduced in the Bupi group compared with the other two groups (P=0.009) whereas time to first postoperative defecation was not different between groups (P=0.70) (Fig. 4A and B). Time to first postoperative flatus and defecation was not influenced by duration of operation, amount of postoperative morphine, or age of patient according to the Cox regression analysis.

The three groups had a similar incidence of nausea and vomiting (Table 3). There were no significant differences in the number of patients requesting antiemetics or the number of doses between groups at 0–24, 24–48, and 48–72 h after the operation (P>0.2 and P>0.2) (Table 4). Side effects were of a mild nature in most patients, except for nine (three in the GA and six in the Saline group) who experienced severe nausea.

There were no significant differences between groups with respect to amount and time to ingestion of food and beverages, from 0–24, 24–48, or 48–72 h after the operation (data not shown).

Most patients had an indwelling bladder catheter, which was removed on the morning after surgery. After removal, two patients, one from the Saline group and one from the Bupi group, complained of urinary retention, lasting a few hours.

Patients fulfilled discharge criteria at median 3 (quartiles 3–4), 4 (3–6), and 5 (3–7) days after operation in the GA-, Saline- and Bupi groups, respectively (ns).

Discussion

The challenge of modern anaesthesia and perioperative medicine is to create efficient treatment regimens with an optimal balance between protective and unwanted effects, in order to ensure patient safety and comfort, and to facilitate recovery.

The main problems of abdominal hysterectomy in the immediate perioperative period are pain, PONV, and gastrointestinal paralysis, which may postpone recovery and discharge from hospital. The optimal anaesthetic regimen for this procedure should carry a low risk, along with effective pain relief and minimal, if not protective, effects on the gastrointestinal dysfunction and PONV induced by surgery. Hence, anaesthetics and analgesics, which produce effective analgesia with a low potential for gastrointestinal side effects, should be advantageous.

This study was designed to investigate whether addition of intraoperative, or intraoperative plus 24 h postoperative epidural analgesia to an opioid-sparing regimen with

Table 3 Percentage of patients with light to severe nausea and percentage who vomited since last assessment in the three groups

	Time after operation (h)							
	0–4	4–6	6–22	22–24	24–26	26–30	30–48	48–72
Light to severe nausea								
GA group	25	30	40	20	30	15	15	15
Saline group	45	15	60	25	15	25	50	20
Bupi group	25	15	30	5	10	25	10	20
Vomited since last assessment								
GA group	15	10	20	5	15	10	15	5
Saline group	10	20	50	15	0	0	10	0
Bupi group	0	5	15	0	5	5	10	5

Table 4 Number of patients who requested antiemetics (ondansetron or metoclopramide), and number of doses administered

	Group			
Postoperative period	**GA group**	**Saline group**	**Bupi group**	***P***
0–24 h				
No. of patients receiving antiemetics	13/20	11/20	10/20	ns
No of doses in patients receiving antiemetics	33	25	16	ns
24–48 h				
No of patients receiving antiemetics	4/20	7/20	4/20	ns
No of doses in patients receiving antiemetics	8	12	4	ns
48–72 h				
No of patients receiving antiemetics	1/20	4/20	1/20	ns
No. of doses in patients receiving antiemetics	1	5	1	ns

paracetamol and NSAID, was able to further reduce pain, improve gastrointestinal function, and enhance recovery.

Results showed a significant reduction in pain and need for supplementary morphine during epidural treatment with bupivacaine. This effect was, however, not sustained beyond the time of the epidural infusion. Gastrointestinal function was only marginally improved, with a minor reduction in time to first postoperative flatus. Side effects, including PONV, were similar in the three study groups, as was recovery as measured by ability to ambulate, oral ingestion of food and fluid, and fulfilment of discharge criteria.

Intraoperative epidural analgesia per se had no influence on postoperative pain or gastrointestinal function compared with the GA group. Hence, no protective analgesic effect of neither a short lasting, nor a 24-h epidural regimen with LA was observed in this study.

Previous studies, in patients undergoing abdominal hysterectomy[8] and colonic surgery,[16–18] have shown that an epidural regimen with LA reduces postoperative pain compared with regimens based on systemic opioids. The present study confirms these results. A longitudinal analysis of variance components, with pain score as the dependent variable, was performed in this study. The covariates, other than treatment group: duration of operation, age of patient, and type of incision were included in the analysis with a hypothesis generating purpose, but none of these showed significant influence on postoperative pain scores. However, it may be that the insignificant results could also be a result of the limited range of covariates and study size.

In contrast to a meta-analysis of previous studies,[8 16 19–21] showing a reduction in time of postoperative gastrointestinal paralysis of about 40 h,[10] the effect of epidural LA on gastrointestinal function in the present study was only small. In contrast to previous studies (except for ref. 17), patients in the GA (control) group in our study received both paracetamol and NSAID, and this opioid-sparing regimen may have reduced gastrointestinal paralysis and thus blunted the effect of epidural anaesthesia. This suggestion, however, has to be confirmed in controlled studies.

No differences in the incidence of side effects was found in this study, but the relative small number of patients in each study group, does not allow firm conclusions.

To be able to evaluate effects of the different regimens on recovery itself, criteria concerning ambulation, oral ingestion of food and fluid, and discharge from hospital were standardized. It should be emphasized, though, that fulfilling discharge criteria did not necessarily mean that patients were actually discharged from hospital. Thus, patients in the GA-, the Saline-, and the Bupi group were actually discharged from hospital on the fourth, fifth, and fifth day, respectively. The most frequent reason for this discrepancy was either a different assessment by the surgeon, or social causes concerning the patient. Still, no differences were observed between groups, and improved analgesia during the first postoperative 24 h was not followed by faster recovery in the Bupi group.

In conclusion, a 24 h postoperative epidural infusion with bupivacaine, when added to postoperative paracetamol and NSAID, reduced pain and opioid requirements, but had no analgesic effects beyond the time of the epidural infusion, and only limited effects on gastrointestinal function and patient recovery after abdominal hysterectomy. Epidural anaesthesia may be superfluous in this surgical procedure.

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Comparison of articaine and bupivacaine/lidocaine for single medial canthus peribulbar anaesthesia

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In a single-centre, randomized, double-blind study, we compared the efficacy of 2% articaine with that of a mixture of 0.5% bupivacaine and 2% lidocaine for peribulbar anaesthesia in cataract surgery, using a single medial canthus injection technique. Eighty-two patients were allocated randomly to receive 7–9 ml of a mixture of 0.5% bupivacaine and 2% lidocaine or an equal volume of 2% articaine with 1:200 000 epinephrine. Hyaluronidase 30 iu ml^{-1} was added to both solutions. The degree of akinesia was scored 1, 5 and 10 min after the block, at the end of surgery and at discharge from the day case unit. Primary outcome measures were the difference in ocular movement scores 5 min after block and the need for supplementary infero-lateral injections. There was greater akinesia in the articaine group at 5 min (P=0.01). Ten patients (24%) in the articaine group and 21 patients (51%) in the bupivacaine/lidocaine group required a supplementary injection (P=0.02). The mean (SD) volume of local anaesthetic required to achieve adequate block for surgery was 9.7 (2.1) ml in the articaine group and 11.0 (2.2) ml in the bupivacaine/lidocaine group (P=0.01). There was a faster offset of akinesia after surgery in the articaine group (P=0.01). There were no differences between groups in the incidence of reported pain or of minor complications. In our study, 2% articaine with 1:200 000 epinephrine was safe and efficacious for single medial canthus peribulbar anaesthesia.

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Articaine is a local anaesthetic synthesized in the 1960s and first investigated clinically in 1974.[1] It is an amide, chemically similar to prilocaine, but it contains a thiophene rather than a benzene ring. It is currently the most widely used local anaesthetic for dental anaesthesia in Germany, Italy and the Netherlands, and has recently been introduced and licensed for dental use in the UK. Articaine's widespread acceptance for dental anaesthesia is due to three main attributes. First, it has low toxicity (maximum recommended dose for dental infiltration is 7 mg kg^{-1}). Secondly, it appears to diffuse through tissues more readily than other local anaesthetic agents. Thirdly, it is metabolized by non-specific plasma esterases in blood and tissue, leading to rapid clearance. After i.v. injection, mean (SD) total body clearance of articaine is 532 (208) litre h^{-1} and the volume of distribution in the central compartment is 2.4 litre kg^{-1} [7.7 (5.1) litre kg^{-1} at steady state].[2] This profile makes articaine an ideal agent for peribulbar anaesthesia, an application that has not been examined previously.

Regional anaesthesia with peribulbar block is the technique of choice for most patients undergoing cataract surgery.[3] A mixture of bupivacaine and lidocaine is the most frequently used local anaesthetic.[4] Limited diffusion of local anaesthetic is the main drawback of peribulbar anaesthesia, leading to failure to achieve eyeball akinesia in up to 50% of patients.[5] This lack of immobility can hinder surgical access. The other main problem with peribulbar anaesthesia is morbidity associated with the injections themselves. The complication rate for globe perforation or haemorrhage has been estimated to be between 0.1 and 1.7%.[6] A single medial canthus injection technique to reduce the morbidity from repeated injections has been described.[7–9] This technique has been shown to be safe, but

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supplementary injections are frequently required because of poor diffusion of local anaesthetic. We postulated that the use of articaine may reduce the need for supplementary injection because of improved diffusion.

Methods

With approval from the Local Research Ethics Committee and informed, written consent, 82 ASA I–III patients scheduled to undergo cataract surgery under local anaesthesia were enrolled in the study. A power calculation predicted a 90% chance of detecting a statistically significant (P<0.05) difference of two points for the sums of the ocular movement scores. Patients were excluded if they were unwilling to take part, had communication problems, were allergic to amide-type local anaesthetic agents, or were known to have low plasma cholinesterase activity ('scoline apnoea' or taking ecothiopate eye drops), as this may affect the metabolism of articaine by plasma esterases.

Patients were allocated randomly to one of two groups using sealed, numbered envelopes and computer randomization with Arcus Quickstat software (CamCode, Cambridge, UK). Group 1 received 2% articaine with 1:200 000 epinephrine and group 2 received a mixture of equal volumes of 0.5% bupivacaine and 2% lidocaine. Hyaluronidase 30 iu ml^{-1} was added to both solutions.

Patients were not fasted and did not receive any premedication.

On arrival in the anaesthetic room, pulse oximetry, non-invasive arterial pressure and electrocardiographic monitoring was started and i.v. access secured. Patients requesting sedation were given alfentanil 250 µg and midazolam 1–2 mg i.v. Oxybuprocaine 0.4% drops were instilled onto the conjunctival sac. One of two consultant anaesthetists, blinded to the local anaesthetic used, performed peribulbar anaesthesia and scored the progression of akinesia. Peribulbar anaesthesia was performed using a single medial canthus injection as described by Ripart and colleagues.[8 9] After test aspiration, local anaesthetic was injected using a 22 mm, 25 G peribulbar short-bevel Atkinson needle (Visitec, Bidford-on-Avon, UK). The maximum injection volume was 9 ml and injection was stopped if signs of proptosis developed. Gentle digital massage of the eyeball was undertaken for 1 min, after which a Honan's balloon, inflated to 30 mm Hg, was applied to facilitate diffusion of local anaesthetic and decrease intra-ocular pressure.

Patients were assessed for ocular and eyelid movements 1, 5 and 10 min after injection, on completion of surgery and before discharge from the day surgery unit, using the scoring system of Brahma and colleagues.[7] Ocular movements were scored for each direction of gaze in the superior, inferior, medial and lateral directions, with a maximum score for each direction of 3 points and a possible total maximum score of 12 points. Eyelid movement was scored, with a maximum score of 2 (Table 1).

Table 1 Scoring system for the degree of akinesia

Ocular movements	
Full movement	3
Moderate movement	2
Flicker	1
No movement	0
Eyelid movement	
Full movement	2
Flicker	1
No movement	0

If after 5 min there was full movement in any direction or a total ocular movement score of 6 or greater, supplementary anaesthesia was provided with an inferolateral injection of 3–5 ml of the test solution. A further inferolateral injection was performed if the block was still inadequate after 10 min. The need for supplementary local anaesthesia and the total volume of local anaesthetic required was recorded. The surgeon, also blinded to the local anaesthetic used, assessed the degree of proptosis and chemosis before surgery and the degree of akinesia and analgesia during surgery. Visual acuity (light perception, hand movement, counting fingers) was assessed at the start of surgery and before discharge. Pain and complications during injection and during surgery were noted. Patients were questioned immediately before discharge about pain during injection and surgery.

Primary outcome measures were the difference in median ocular and eyelid movement scores at 5 min and the need for supplementary local anaesthesia. Secondary outcome measures were ocular and eyelid movement scores at 1 and 10 min, the end of surgery and on discharge, total volume of local anaesthetic used, and complications.

Statistical analysis of data, using Arcus Quickstat software, involved a two-tailed Student's t-test for age, axial length and total volume of local anaesthetic and the χ^2 test or Fisher's exact test for sex, supplementary injections, complications and visual acuity. A two-tailed Wilcoxon rank sum test was used for comparing ocular and eyelid movement scores. P<0.05 was considered statistically significant.

Results

There were 41 patients in each group and all patient data were included in the statistical analysis. No patients met the exclusion criteria for the study. There were no significant differences in patient characteristics between the two groups (Table 2).

Median ocular movement scores were significantly reduced in group 1 at 5 min (P=0.01) (Fig. 1). Ten patients (24%) in group 1 required supplementary local anaesthesia compared with 21 patients (51%) in group 2 (P=0.02). One patient in group 2 required a third injection. There was no significant difference in median ocular movement scores at

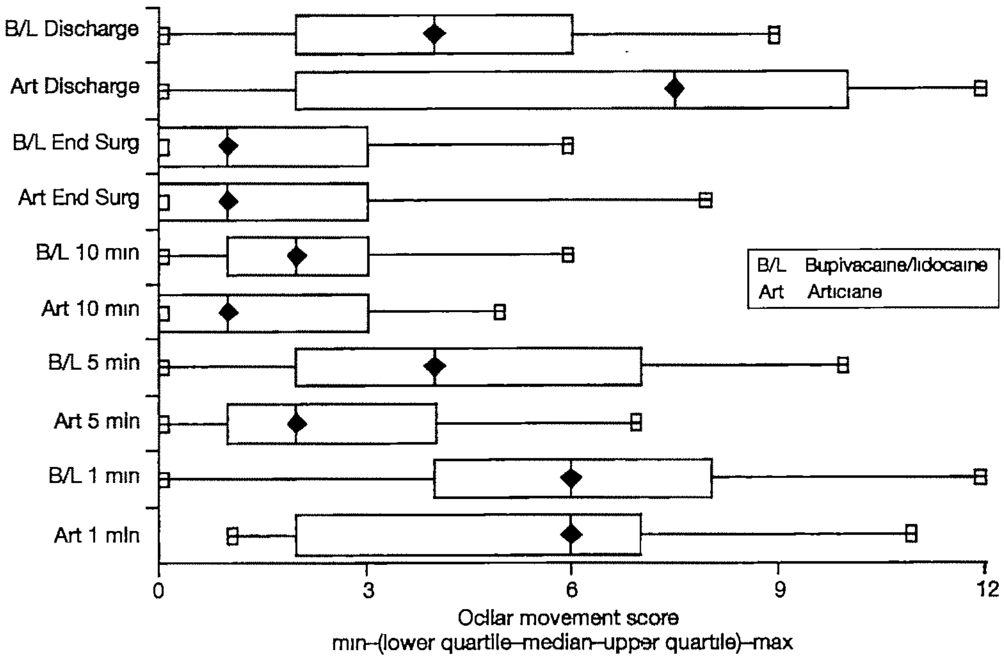

Fig 1 Median (interquartile range and range) ocular movement scores. Art = articaine; B/L = bupivacaine/lidocaine. Significant differences at 5 min (P=0.01) and discharge (P<0.01).

Table 2 Patient characteristics Values are mean (SD) where appropriate

	Group 1 Articaine 2% (n=41)	Group 2 Bupivacaine 0.5% + lidocaine 2% (n=41)	P
Age (yr)	75.3 (9.6)	76.7 (9.0)	0.50
Male:female	14:27	22:19	0.12
Axial length (mm)	23.5 (1.0)	23.3 (0.9)	0.28

Table 3 Ocular and eyelid movement scores Values are median (interquartile range)

	Group 1 Articaine 2% (n=41)	Group 2 Bupivacaine 0.5% + lidocaine 2% (n=41)	P
Ocular movement score			
1 min	6 (2–7)	6 (4–8)	0.11
5 min	2 (1–4)	4 (2–7)	0.01
10 min	1 (0–3)	2 (1–3)	0.14
End of surgery	1 (0–3)	1 (0–3)	0.78
Discharge	7 (3–10)	4 (2–6)	0.01
Eyelid movement score			
1 min	1 (0–1)	1 (1–2)	0.02
5 min	0 (0–1)	0 (0–1)	0.02
10 min	0 (0)	0 (0–1)	0.06
End of surgery	1 (0–1)	1 (0–2)	0.05
Discharge	2 (1–2)	2 (0–2)	0.23

Table 4 Surgeon's assessment of akinesia during surgery

	Group 1 Articaine 2% (n=41)	Group 2 Bupivacaine 0.5% + lidocaine 2% (n=41)
Good	35	31
Adequate	6	7
Poor	0	3

Table 5 Complications during injection and surgery

	Group 1 Articaine 2% (n=41)	Group 2 Bupivacaine 0.5% + lidocaine 2% (n=41)	P
Injection			
Chemosis	19	17	0.8
Haematoma (mild)	1	0	1
Discomfort	17	11	0.4
Surgery			
Proptosis	2	1	1
Chemosis	6	3	0.5

1 min, 10 min and at the end of surgery. Median eyelid opening scores were lower in group 1 at 1 and 5 min (P=0.02) (Table 3). The mean (SD) time from initial injection to the end of surgery was 44 (14) min in group 1 and 42 (13) min in group 2 (P=0.56). The mean (SD) time from insertion of the block to discharge assessment was 104 (25) min in group 1 and 114 (30) min in group 2 (P=0.2). The ocular movement score was significantly higher in group 1 before discharge from the day case unit (P<0.01). The mean (SD) total volume of local anaesthetic was 9.7

(2.1) ml in group 1 and 11.0 (2.2) ml in group 2 (P=0.01). There was no significant difference in visual acuity between groups at the start of surgery or on discharge.

One patient in group 2 complained of pain during surgery, which was treated with oxybuprocaine drops to the conjunctiva. On specific questioning before discharge, six patients in group 1 and eight patients in group 2 reported minimal pain during surgery, which they had not mentioned at the time of surgery.

Discussion

The technique of single medial canthus injection has several possible advantages over dual injection techniques. These include decreased pain and risk of globe perforation with single needle insertion and injection in an avascular area, reducing the risk of haemorrhage or intravascular injection. These advantages are reduced if a supplementary injection is required. In our study, the number of patients in the articaine group requiring a second injection was 24% compared with 51% in the bupivacaine/lidocaine group (P=0.02). This may reflect better diffusion of articaine from the medial orbital compartment to the eyelids and muscle cone. Ripart and colleagues[8] reported a supplementary injection rate of 9.27% at 15 min using 0.5% bupivacaine alone or with 1% etidocaine or 2% lidocaine, plus hyaluronidase 25 iu ml^{-1}. They reported a learning curve: in the first 30 patients, 26.6% required a supplementary injection. Brahma and colleagues[7] found that a single medial canthus injection using prilocaine 3% with felypressin provided a safe and effective peribulbar block. Their re-block rate, using timing and criteria for supplementary injection similar to those in our study, was 9.7%. However, they used hyaluronidase 125 iu ml^{-1}, whereas we used 30 iu ml^{-1}. We discontinued the use of prilocaine after the manufacturer issued a report in January 2000 of three cases of optic atrophy and one of cilioretinal occlusion after the use of 3% prilocaine with felypressin for peribulbar anaesthesia.

The ideal agent for peribulbar anaesthesia must be safe and give a rapid onset of anaesthesia, a dense motor block and an adequate duration of action for surgery, but must not prolong akinesia.[10 11] We have demonstrated that articaine satisfies many of these criteria. Articaine has a wider therapeutic index than lidocaine whilst having similar potency.[2] In our study, articaine had a more rapid onset of action, resulting in better akinesia at 5 min than a bupivacaine/lidocaine mixture. There was less requirement for a supplementary injection. The likelihood of complications was therefore reduced. Our surgeon did not assess akinesia during surgery as poor in any of the patients in the articaine group (Table 4). The duration of block was adequate for surgery in all cases. Articaine had a faster offset than bupivacaine/lidocaine, with quicker return of protective reflexes and less likelihood of inadvertent damage to an anaesthetized eye when the patient was discharged after surgery.

In summary, our study suggests that 2% articaine with epinephrine 1:200 000 is as safe as and more efficacious than a mixture of 0.5% bupivacaine and 2% lidocaine for single medial canthus peribulbar anaesthesia (Table 5). There is a lower risk of globe perforation as a result of a lower requirement for supplementary injection. Fewer supplementary injections before surgery and quicker return of protective reflexes after surgery can result in a faster throughput of patients having cataract surgery. Articaine is less expensive than bupivacaine at current UK prices.

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Prospective randomized, double-blind comparative study of dexamethasone, ondansetron, and ondansetron plus dexamethasone as prophylactic antiemetic therapy in patients undergoing day-case gynaecological surgery

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Dexamethasone alone and in combination with selective 5-hydroxytryptamine receptor antagonists is of benefit in the prophylaxis of post-operative nausea and vomiting. In this study, the effectiveness of such a combination in comparison to either drug alone is investigated in day case gynaecological surgery. A total of 177 patients were randomized to three treatment groups: dexamethasone 8 mg, ondansetron 4 mg, and dexamethasone 8 mg plus ondansetron 4 mg. The only significant difference between groups was seen in the first 3 h when failure of prophylaxis was more frequent in patients who had received dexamethasone alone (P=0.0085; Fisher's exact probability test). Confidence interval analysis indicates a modest treatment effect for the combination and the decision whether to perform a larger study depends upon whether such an effect is clinically relevant.

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A recent meta-analysis examined the role of dexamethasone for the prevention of postoperative nausea and vomiting.[1] It concluded that 'it is very likely that the best prophylaxis of postoperative nausea and vomiting (PONV) currently available is by combining dexamethasone with a selective 5-hydroxytryptamine type 3 (5-HT$_3$) receptor antagonist'. Such combinations are both safe and efficacious in paediatric,[2 3] obstetric,[4] breast,[5] middle ear,[6] and other[7] surgery associated with a high risk of PONV. Despite work demonstrating the benefits of such combination therapy in major gynaecological surgery,[8–11] little evidence exists regarding the use of an ondansetron and dexamethasone combination in a day-surgical gynaecological population.[12]

PONV occurs frequently after day case gynaecological surgery.[13–15] Both 5-HT$_3$ receptor antagonists[14 16] and dexamethasone[17] are superior to placebo in the prophylaxis of PONV in this setting. Our study has compared the efficacy of ondansetron plus dexamethasone with each antiemetic alone for the prevention of PONV in patients undergoing day case gynaecological surgery.

Patients and methods

After obtaining approval from the local research ethical committee and written informed consent, we studied 177 ASA I or II pre-menopausal female patients, aged 19–53 yr, undergoing day case gynaecological surgery. Patients with gastrointestinal, liver, or renal diseases, those who had received any antiemetic medication within 24 h before surgery or complained of pre-operative nausea or vomiting, and those who were pregnant, lactating or with a body mass index of greater than 35 were excluded.

Patients were allocated randomly to receive one of three treatment regimens: ondansetron 4 mg, dexamethasone 8 mg, or ondansetron 4 mg with dexamethasone 8 mg. A randomization list was prepared using a mechanical randomization device. The drugs were administered by slow i.v. injection immediately after induction of anaesthesia. Personnel not involved in the study prepared identical syringes containing the study drug(s). The drug(s) were diluted with normal saline to achieve a volume of 5 ml. The study drugs are known to be compatible when mixed.[18]

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A standardized anaesthetic technique was used. This was administered by one of the two investigators who were unaware of which treatment the patient had been given. Patients received no pre-anaesthetic medication. Anaesthesia was induced with 2.0–2.5 mg kg^{-1} propofol and 1 µg kg^{-1} fentanyl and maintained with 2.0–3.0% sevoflurane (inspired concentration) and 66% nitrous oxide in oxygen. Ventilation was controlled mechanically via a laryngeal mask airway (LMA[†]) and adjusted to maintain end-tidal carbon dioxide concentration at 4.5–5.3 kPa throughout surgery. Neuromuscular relaxation was achieved with mivacurium 0.1–0.2 mg kg^{-1} and was not reversed. All patients received a 100 mg diclofenac suppository before surgery started. In addition, tramadol 100 mg i.v. was administered to those patients who underwent laparoscopic procedures.

Patients were transferred to the recovery area once adequate spontaneous respiration was established and the LMA was removed once the patient was awake. Whilst in recovery, rescue analgesia was provided by a further dose of tramadol 100 mg i.v. if required. If patients experienced PONV whilst in hospital, cyclizine 50 mg i.m. was administered as rescue antiemesis. On discharge home, patients were provided with cyclizine 50 mg tablets to be taken if needed. All patients were discharged with a 3-day supply of analgesics. Those who had undergone laparoscopic procedures were provided with diclofenac 50 mg and codeine phosphate 30 mg/paracetamol 500 mg tablets. Other patients were provided with dextropropoxyphene 32.5 mg/paracetamol 325 mg tablets. Patients were advised to take their analgesic medication regularly for the first 24 h post-discharge.

Table 1 Patient characteristics. Values are numbers or means (SD)

Group	Dexamethasone	Ondansetron	Combination
n	60	59	58
Age (yr)	34.9 (20–50)	36.2 (21–53)	36.0 (19–53)
Body mass index	25.1 (4.2)	23.8 (3.5)	24.1 (3.3)
Past history of PONV or travel sickness	35	34	33
Non-smokers	40	41	32
Migraine sufferers	20	18	18
Menstruation	4	9	8
Duration of anaesthesia (min)	30.5 (9.94)	29.7 (7.41)	30.2 (9.3)
Laparoscopic procedure	33	33	38
Laparoscopic sterilization	13	18	14
Procedure involving cervical dilation	53	52	55
Rescue analgesia provided in recovery (tramadol)	3	4	6

Table 2 Incidence of nausea, retching, vomiting, use of rescue antiemetics and patients in whom prophylaxis failed. Values are numbers (proportions)

		Dexamethasone	Ondansetron	Combination
Group 0–3 h				
	Nausea	16	13	5
	Retching	5	1	1
	Vomiting	4	0	1
	Rescue antiemetic	8	7	2
Overall proportion of subjects classified as 'failures'		17/60 (0.283)	13/59 (0.22)	5/58 (0.086)
Combination *vs* dexamethasone: 0.2 (95% CI: 0.06 to 0.33, 99% CI: 0.01 to 0.37)				
Combination *vs* ondansetron: 0.13 (95% CI: 0.01 to 0.27)				
Ondansetron *vs* dexamethasone: 0.063 (95% CI: –0.09 to 0.22)				
Group 3–12 h				
	Nausea	20	16	14
	Retching	4	1	1
	Vomiting	6	4	3
	Rescue antiemetic	16	12	12
Overall proportion of subjects classified as 'failures'		21/60 (0.35)	18/59 (0.305)	14/58 (0.241)
Combination *vs* dexamethasone: 0.11 (95% CI: –0.06 to 0.27)				
Combination *vs* ondansetron: 0.064 (95% CI: –0.10 to 0.22)				
Ondansetron *vs* dexamethasone: 0.045 (95% CI: –0.12 to 0.21)				
Group 12–24 h				
	Nausea	7	6	8
	Retching	0	0	0
	Vomiting	0	1	0
	Rescue antiemetic	7	7	8
Overall proportion of subjects classified as 'failures'		9/60 (0.15)	8/59 (0.135)	9/58 (0.155)

Patients were interviewed on discharge from the day surgical unit (3 h post-surgery) by blinded nursing staff and by phone at 24 h post-surgery by one of the two blinded investigators. The patients were asked if retching or vomiting had occurred, whether rescue antiemetics had been used and if they had felt nauseated in three time periods: 0–3, 3–12, and 12–24 h post-surgery, with only two possible answers (yes/no). Nausea was defined as the unpleasant sensation associated with awareness of the urge to vomit; retching was defined as laboured, spasmodic, rhythmic contraction of the respiratory muscles without expulsion of gastric contents; vomiting was defined as the forceful expulsion of gastric contents from the mouth.[19] Failure of prophylaxis was defined as any episode of nausea, retching, vomiting or use of rescue antiemetic. The nursing staff and investigators recorded details of adverse events using an open questioning technique. The patients were asked about analgesic consumption after leaving hospital and pain was scored at 3 and 24 h using a simple scoring system (1, no pain; 2, mild pain; 3, moderate pain; 4, severe pain).

A sample-size of 174 patients (58 in each of three treatment groups) was required to detect a difference in response rates of 0.25 from a baseline prevalence of 0.5, with 80% power at a two-sided significance level of 5%. Sample size was determined using the software package nQuery Advisor v 3.0 (Statistical Solutions Ltd, Cork, Ireland). The progress of the study was monitored by an independent third party who kept a record of numbers per treatment group and terminated the study when a minimum of 58 patients in each group was obtained.

Table 3 Incidence of adverse effects. Values are numbers

Group	Dexamethasone	Ondansetron	Combination
Fatigue	1	4	2
Dizziness	1	2	3
Headache	1	2	1
Pruritus	1	1	0
Flushing	0	0	3
Cough	0	0	1
Diarrhoea	0	1	0
Transient chest pain	2	0	0
Heartburn	1	0	0

The statistical significance of observed differences in the treatment outcomes was assessed using the recommended method (Wilson[20]) for comparing two proportions in the software package Confidence Interval Analysis v. 2.0.0 (BMJ Books, 2000). To make allowances for multiple testing, all differences found to be significant at the 5% level were re-tested at the 1% level (using 99% confidence interval). Thence, the exact probability of any differences surviving such tests was obtained using Fisher's exact test (StatXact v. 3.0, Cytel Software Corporation, MA, USA).

Results

Patient characteristics and surgical procedures were similar in each group (Table 1). Failure of prophylaxis during the first 3 h (0–3 h) after surgery was recorded in 22, 28.3, and 8.6% of patients who had received ondansetron, dexamethasone, and ondansetron/dexamethasone, respectively. The incidences during the next 9 h (3–12) were 30.5, 35, and 24.1%, respectively. The incidences during the following 12 h (12–24) were 13.5, 15, and 15.5%, respectively. The overall incidences for the 24 h post surgery were 42.4, 48.3, and 34.5%, respectively.

Thus, only in the first 3 h was failure of prophylaxis seen significantly less often in patients who had received a combination of ondansetron and dexamethasone than in those who had received dexamethasone alone: exact probability P=0.0085. For ondansetron, the difference was significant at the 5% level, but not by our stricter 1% criterion (see Table 2). No patient required hospital admission for PONV. The most frequently reported adverse events were fatigue, headache, and dizziness, but there were

Table 4 Incidence and severity of pain and use of opiate analgesia after hospital discharge Values are numbers

		Dexamethasone	Ondansetron	Combination
Group at 3 h				
	No pain	25	30	28
	Mild pain	24	21	22
	Moderate pain	11	7	8
	Severe pain	0	1	0
Group at 24 h				
	No pain	21	22	21
	Mild pain	25	25	26
	Moderate pain	14	10	11
	Severe pain	0	1	0
Use of opiate analgesia after hospital discharge in first 24 hrs (either codeine phosphate or dextropropoxyphene)		47	43	46

no differences between groups (Table 3). There were no differences with respect to analgesic consumption and the incidence and severity of pain (Table 4).

Discussion

The aetiology of PONV after gynaecological surgery performed under general anaesthesia remains elusive, but is probably multifactorial. Age, gender, smoking habits, past history of previous PONV and/or motion sickness, surgical procedure, length of procedure, and use of postoperative opioids are of importance in predicting PONV.[21–23] In our study, these factors were well balanced between groups and, therefore, differences between groups may be attributed to differences in the antiemetic drugs administered. We decided to include a heterogeneous group of operations in our study to increase the ability to generalize our findings. Although theoretically, the baseline incidences of and mechanisms for PONV may be different for different operations, evidence for this is lacking in the group of operations we included.[23] We did specifically exclude the procedures of dilation and curettage and termination of pregnancy, as the incidence of PONV is lower.[23]

As PONV is recognized to be a common complication of gynaecological surgery performed under general anaesthesia,[24] we did not believe it to be ethical to include a placebo arm in our study. We based our choice of a baseline prevalence for PONV of 0.5 on the findings of other studies[8 10 13 24] and on local audit data. The high incidence of PONV in this population may justify the use of prophylactic antiemetics. Using antiemetics in this way, however, does raise cost-effectiveness issues.[25] At the drug dosages used, we found that ondansetron and dexamethasone performed similarly, despite an approximate 7-fold price differential. Our selection of drug dosages was based on previous work that demonstrated that these doses were effective.[26 27]

Our study demonstrated a significant difference between the ondansetron/dexamethasone combination and either drug alone in the 0–3 h period. Although this difference failed to maintain significance overall (0–24 h), or during the 3–12 or 12–24 h periods, the 95% confidence intervals show a trend suggesting that the combination has some benefit over the individual drugs. This is probably a result of underpowering of our study for the size of the actual difference observed. In designing this study, we had to choose an arbitrary reduction in PONV that we believed clinically important. We based this upon a reduction of 50% in the incidence of PONV in the combination group when compared with either of the single treatment groups. We believed this to be a reasonable and clinically important effect that would lead to anaesthetists using the ondansetron/dexamethasone combination in preference to either drug alone.

Our failure to demonstrate significance overall (0–24 h) may be because of other reasons. It could be argued that our base line prevalence for PONV of 0.5 was too high, in the absence of a placebo group. This would result in an underestimation of sample size. The fact that the dexamethasone treatment group demonstrated a PONV rate of 0.48 would argue against this, however. Additionally, we may have reduced the likelihood of a significant result by our decision to include a heterogeneous group of operations. This decision has been discussed above. It may be that a smaller than 50% reduction in PONV as a result of using the combination therapy in preference to single agent therapy is still clinically valuable. This is in the context of a day case gynaecological population as a whole or for certain high risk patients within it. We estimate that 1565 patients per group would be required in an identical study of the same power investigating a 10% difference between treatment groups.

Other work has suggested that dexamethasone alone[28] or in combination,[1 12] may be particularly efficacious in preventing late or delayed PONV. Our results do not support this, but this may be because of problems associated with our study design as discussed above.

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BJA

LABORATORY INVESTIGATIONS

Small dose of exogenous surfactant combined with partial liquid ventilation in experimental acute lung injury: effects on gas exchange, haemodynamics, lung mechanics, and lung pathology

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A combination of exogenous surfactant and partial liquid ventilation (PLV) with perfluorocarbons should enhance gas exchange, improve respiratory mechanics and reduce tissue damage of the lung in acute lung injury (ALI). We used a small dose of exogenous surfactant with and without PLV in an experimental model of ALI and studied the effects on gas exchange, haemodynamics, lung mechanics, and lung pathology. ALI was induced by repeated lavages ($Pa_{O_2}/F_{I_{O_2}}$ less than 13 kPa) in 24 anaesthesized, tracheotomized and mechanically ventilated ($F_{I_{O_2}}$ 1.0) juvenile pigs. They were treated randomly with either a single intratracheal dose of surfactant (50 mg kg^{-1}, Curosurf®, Serono AG, München, Germany) (SURF-group, n=8), a single intratracheal dose of surfactant (50 mg kg^{-1}, Curosurf®) followed by PLV with 30 ml kg^{-1} of perfluorocarbon (PF 5080, 3M, Germany) (SURF-PLV-group, n=8) or no further intervention (controls, n=8). Pulmonary gas exchange, respiratory mechanics, and haemodynamics were measured hourly for a 6 h period. In the SURF-group, the intrapulmonary right-to-left shunt ($\dot{Q}_S/\dot{Q}_T$) decreased significantly from mean 51 (SEM 5)% after lavage to 12 (2)%, and Pa_{O_2} increased significantly from 8.1 (0.7) to 61.2 (4.7) kPa compared with controls and compared with the SURF-PLV-group (P<0.05). In the SURF-PLV-group, $\dot{Q}_S/\dot{Q}_T$ decreased significantly from 54 (3)% after induction of ALI to 26 (3)% and Pa_{O_2} increased significantly from 7.2 (0.5) to 30.8 (5.0) kPa compared with controls (P<0.05). Static compliance of the respiratory system (C_{RS}), significantly improved in the SURF-PLV-group compared with controls (P<0.05). Upon histological examination, the SURF-group revealed the lowest total injury score compared with controls and the SURF-PLV-group (P<0.05). We conclude that in this experimental model of ALI, treatment with a small dose of exogenous surfactant improves pulmonary gas exchange and reduces the lung injury more effectively than the combined treatment of a small dose of exogenous surfactant and PLV.

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Deficiency of alveolar surfactant, pulmonary hypertension, intrapulmonary right-to-left shunting, and poor arterial oxygenation are features of both experimental acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS).[1] Loss of surfactant increases surface tension, end-expiratory alveolar collapse, and atelectasis.

Mechanical ventilation can further damage the alveolo-capillary unit by overdistension, and cyclic collapse and re-opening of terminal airways.[2–5] Mechanical ventilation with

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tidal volumes of 6 ml kg^{-1}, a positive end-expiratory pressure (PEEP) level above the lower inflection point, and a peak inspiratory pressure below the upper inflection point may protect against this effect.[2,6] Other treatments to reduce the mechanical shear stress of the lung include surfactant replacement,[7–11] partial liquid ventilation (PLV),[12–17] and extracorporal membrane oxygenation (ECMO).[18] Giving surfactant may reduce surface tension, improve gas exchange and lung mechanics.[7–11] In PLV the lung is partially filled with a perfluorocarbon and conventional mechanical ventilation is resumed. PLV can improve gas exchange and lung mechanics without significantly affecting systemic circulation.[12–17]

Exogenous surfactant and PLV have been investigated using different doses and different experimental models of ALI.[19–29] The effects on gas exchange, haemodynamics, lung mechanics, and lung damage were variable.

A combination of 100 mg kg^{-1} of surfactant with PLV, restored pulmonary gas exchange more efficiently in an experimental model of neonatal ALI than surfactant therapy alone. However, a combination of PLV with only 5 mg kg^{-1} of surfactant failed to give additional benefit compared with PLV alone.[27,29]

We compared a single dose of 50 mg kg^{-1} surfactant alone *vs* 50 mg kg^{-1} surfactant combined with PLV in a pig model of ALI, with measurements of gas exchange, haemodynamics, respiratory mechanics, and progression of lung injury.

Methods

This study was approved by the Berlin Animal Protection Committee in accordance with German Animal Protection Law, and conforms with the Guide for the Care and Use of Laboratory Animals (DHHS, PHS, NIH Publication No. 85-23).

General experimental procedures

We studied 24 piglets (weight 23–27 kg), aged between 6 and 8 weeks. Anesthesia was induced with thiopental (10 mg kg^{-1} i.v.) and fentanyl (10 μg kg^{-1} i.v. followed by an infusion of 0.05–0.08 μg kg^{-1} min^{-1}). Muscle relaxation was obtained with pancuronium bromide (0.15 mg kg^{-1} i.v. bolus, followed by a continuous infusion of 2.5 μg kg^{-1} min^{-1}). Immediately after induction, the pigs were tracheotomized and intubated with a 9.0 mm outer diameter tracheal tube, fitted with a heat and moisture exchanger.

The animals were placed supine and ventilated in a volume controlled mode (tidal volume 10–12 ml kg^{-1}, respiratory rate 16 min^{-1}, FI_{O_2} 1.0, I:E ratio 1:1, PEEP 5 cm H_2O) with an EVITA 2 model 76 ventilator (Dräger, Lübeck, Germany). Core temperature was maintained within ±0.5°C of the pre-study value using a heating pad. No drugs were used to support the circulation.

We placed a pulmonary artery catheter (model 93A-431-7.5 Fr, Baxter Healthcare Corporation, Irvine, CA, USA) percutaneously via the femoral vein, and an arterial cannula (18 G; Vygon, Ecouen, France) into the femoral artery, for blood sampling and haemodynamic measurements. Heart rate (HR), central venous pressure (CVP), mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), and pulmonary artery wedge pressure (PCWP) were recorded using a Hewlett-Packard monitoring system (Model 66 S, Böblingen, Germany). Measurements were taken with pigs in the supine position with zero at the level of the midaxilla. Vascular pressures were the average taken at end-expiration of three successive respiratory cycles. Cardiac output (CO) was determined by thermodilution using the mean of four measurements (10 ml saline at 1–5°C) arbitrarily performed during different phases of the respiratory cycle. Intrapulmonary shunt ($\dot{Q}S/\dot{Q}T$), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) were calculated using standard formulae.

All blood samples (arterial and mixed venous) were collected anaerobically, and analysed within 5 min (ABL 520, Radiometer, Copenhagen, Denmark). Arterial oxygen saturation (Sa_{O_2}) and mixed venous oxygen saturation ($S\bar{v}_{O_2}$) were measured by spectrophotometry with the analyser calibrated with pig blood (OSM 3 Hemoximeter, Radiometer). Static compliance of the respiratory system (C_{RS}) was determined using automated inspiratory, repetitive occlusions (1 s) at single volume steps (SCASS).[30] Measurements started with 10 ml *Vt* up to a maximum *Vt* of 10–12 ml kg^{-1}, using volume steps of 10 ml each. C_{RS} was calculated as mean of all generated pressure–volume curves from the inspiratory limb.

Lung tissue from all animals was examined histologically. After killing the animals, the tracheal tube was clamped at end-expiration (PEEP 5 cm H_2O) and the lungs were removed. Perfluorocarbon was left *in situ* in animals treated with PLV. Tissues were fixed in 5% formalin. Specimens from the cranial ventral (non-dependent) and caudal dorsal (dependent) lobes were stained with haematoxylin and eosin and then scored using a semiquantitative scoring system by an experienced veterinary pathologist (A. S-K.), blinded to treatment, for interstitial infiltration, interstitial oedema, emphysema, and atelectasis. Each variable was scored using a 0–4-point scale, with no injury scored 0, injury in 25% of the field scored 1, injury in 50% of the field scored 2, injury in 75% of the field scored 3, and injury throughout the field scored 4. The total score maximum was 16.

Induction of ALI

Repeated lavage with warmed isotonic saline (37°C) was done to produce lung surfactant depletion as reported by Lachmann and co-workers, and described in detail elsewhere.[31,32] Induction of ALI was assumed when the Pa_{O_2}/FI_{O_2} ratio was persistently less than 13 kPa for 1 h.

Table 1 Time course of HR, MABP, MPAP, CO, SVR, and PVR during baseline (pre-lavage), after induction of ALI (post-lavage), and for 6 h thereafter, in controls (n=8 at ALI, four pigs died before 6 h after ALI), in pigs treated with a single intratracheal dose of 50 mg kg^{-1} of surfactant (Curosurf®) after induction of ALI (SURF-group) (n=8 pigs, none died), and in pigs treated with a single intratracheal dose of 50 mg kg^{-1} of surfactant (Curosurf®) followed by PLV with 30 ml kg^{-1} of perfluorocarbon (PF 5080) after induction of ALI (SURF-PLV-group) (n=8 pigs, none died). Data are mean (SEM) *Intergroup comparison*: controls *vs* SURF-PLV-group and controls *vs* SURF-group *$P<0.05$, and SURF-PLV-group *vs* SURF-group †$P<0.05$ (Kruskal–Wallis ANOVA and post hoc Dunn's test) *Intragroup comparison*: data measured after induction of ALI *vs* data obtained at hourly intervals thereafter ‡$P<0.05$ (Friedman test and post hoc Dunn's test)

	Group	HR (beats min^{-1})		MABP (mm Hg)		MPAP (mm Hg)		CO (litre min^{-1})		SVR (dyn s cm^{-5})		PVR (dyn s cm^{-5})	
		Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Baseline	SURF	77	4	102	5	20	1	3.6	0.2	2081	119	149	30
	SURF-PLV	95	5	99	5	23	1	3.8	0.5	2026	285	241	52
	Controls	95	9	88	5	20	1	3.6	0.3	1827	201	165	25
ALI	SURF	102	11	94	4	25	1	4.4	0.6	1650	210	266	49
	SURF-PLV	102	6	94	5	28	2	4.4	0.4	1593	191	268	28
	Controls	93	6	89	6	28	2	3.8	0.2	1718	227	301	53
1 h	SURF	92	10	91	4	27	2	3.7	0.3	1769	150	335	63
	SURF-PLV	100	6	92	6	32	2	4.0	0.3	1614	160	366	38
	Controls	93	5	87	7	30	2	3.9	0.4	1688	243	329	49
2 h	SURF	88	9	92	6	28	2	3.4	0.3	1930	163	392	60
	SURF-PLV	89	5	94	5	34‡	2	3.5	0.3	1944	229	466	76
	Controls	93	7	83	7	35	2	3.4	0.2	1697	194	466	33
3 h	SURF	86	9	98	6	30	2	2.8‡	0.3	2573	186	525‡	73
	SURF-PLV	88	6	93	2	36‡	1	3.1‡	0.3	2145	192	578‡	79
	Controls	100	10	87	8	36	2	3.8	0.4	1767	279	486	50
4 h	SURF	77	5	99	5	30*	2	2.6‡	0.2	2723	176	592‡	79
	SURF-PLV	90	5	91	4	38†‡	1	2.9‡	0.3	2278	258	667‡	69
	Controls	97	10	89	9	39‡	2	3.7	0.3	1845	326	563	70
5 h	SURF	79	8	99	5	29*	2	2.6‡	0.3	2831	207	581‡	98
	SURF-PLV	93	11	88	6	39†‡	1	3.2‡	0.4	2009	290	663‡	104
	Controls	102	9	81	9	41‡	3	3.5	0.4	1742	323	596‡	100
6 h	SURF	80	8	97	5	30*	3	2.6‡	0.2	2662	188	560‡	83
	SURF-PLV	95	8	82	7	40†‡	1	3.1‡	0.3	1857	337	659‡	82
	Controls	109	7	74‡	11	41‡	3	3.5	0.5	1601	427	627	110

Experimental procedure

After induction of ALI, the animals were randomly assigned to receive a single intratracheal dose of surfactant alone (50 mg kg^{-1}, Curosurf®) (SURF-group, n=8), or a single intratracheal dose of surfactant (50 mg kg^{-1}), followed after 30 min by 30 ml kg^{-1} of perfluorocarbon (PF 5080, 3M, Germany) (SURF-PLV-group, n=8), or no further intervention (controls, n=8). Evaporative losses of PF 5080 were replaced at a dose of 4 (3) ml kg^{-1} every hour as previously found by our group.[33]

PF 5080 (C_8F_{18}) is a non-ozone-depleting PFC with boiling point 102°C, density (at 25°C) 1.76 g ml^{-1}, viscosity (at 25°C) 1.4 cp, vapour pressure (at 37°C) 6.8 kPa, solubility of oxygen (at 37°C) 49 ml 100 ml^{-1}, solubility of carbon dioxide (at 37°C) 176 ml 100 ml^{-1}, and surface tension (at 25°C) of 15 dyn s cm^{-1} (information taken from 3M data sheet). Curosurf® is isolated from minced pig lungs and contains 99% lipids, mainly phospholipids, and 1% low molecular weight hydrophobic apoproteins SP-B and SP-C.[16]

Statistical analysis

Results are expressed as mean (SEM). The data were obtained at baseline (pre-lavage), immediately after the induction of ALI (post-lavage) and at hourly intervals for 6 h thereafter. Statistical analysis was performed using SPSS for Windows 8.0 and Sigmastat (SPSS Inc., Chicago, IL, USA). Differences between groups were evaluated using Kruskal–Wallis ANOVA followed by post hoc comparisons with Dunn's test (intergroup comparison). The Friedman test was used to compare the data after induction of ALI with the data measured during the subsequent 6 h (intragroup comparison). For post hoc testing, Dunn's test also was applied. Statistical significance was assumed at $P<0.05$.

Results

All animals were comparable with regard to body weight and pre-study conditions. Pre-lavage data of pulmonary gas exchange, lung compliance, and haemodynamics did not differ significantly between groups (Tables 1 and 2).

In all animals, induction of ALI increased $\dot{Q}s/\dot{Q}t$ concomitant with a decrease in Pa_{O_2}. Cardiac output (CO), mean pulmonary artery pressure (MPAP), and pulmonary vascular pressure (PVR) increased while mean arterial blood pressure (MABP), and systemic vascular resistance (SVR) decreased (Tables 1 and 2).

Table 2 Time course of intrapulmonary shunting ($\dot{Q}s/\dot{Q}t$), arterial oxygen tension (Pa_{O_2}), arterial carbon dioxide tension (Pa_{CO_2}), arterial pH (pH_a), oxygen delivery (D_{O_2}), oxygen consumption ($\dot{V}_{O_2}$), static compliance of the respiratory system (C_{RS}), and survivors during baseline (pre-lavage), after induction of ALI (post-lavage), and for 6 h thereafter, in controls (n=8 at ALI, four pigs died before 6 h after ALI), in pigs treated with a single intratracheal dose of 50 mg kg^{-1} of surfactant (Curosurf®) after induction of ALI (SURF-group) (n=8 pigs, none died), and in pigs treated with a single intratracheal dose of 50 mg kg^{-1} of surfactant (Curosurf®) followed by PLV with 30 ml kg^{-1} of perfluorocarbon (PF 5080) after induction of ALI (SURF-PLV-group) (n=8 pigs, none died). Data are mean (SEM). *Intergroup comparison:* controls *vs* SURF-PLV-group and controls *vs* SURF-group: *P<0.05, and SURF-PLV-group *vs* SURF-group †P<0.05 (Kruskal–Wallis ANOVA and post hoc Dunn's test). *Intragroup comparison* data measured after induction of ALI *vs* data obtained at hourly intervals thereafter: ‡P<0.05 (Friedman test and post hoc Dunn's test)

	Group	$\dot{Q}s/\dot{Q}t$ (%)		Pa_{O_2} (kPa)		Pa_{CO_2} (kPa)		pHa		D_{O_2} (ml min^{-1})		$\dot{V}_{O_2}$ (ml min^{-1})		C_{RS} (ml mbar^{-1})		Survivors (n)
		Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	
Baseline	SURF	12	1	75.7	3.2	4.7	0.5	7.56	0.03	423	28	142	14	22	1.0	8
	SURF-PLV	16	3	68.0	3.8	5.5	0.4	7.48	0.02	418	50	143	21	21	1.8	8
	Controls	16	3	72.7	3.6	6.1	0.7	7.43	0.04	396	26	110	10	23	1.0	8
ALI	SURF	51	5	8.1	0.7	6.1	0.6	7.42	0.04	361	34	134	16	9	0.6	8
	SURF-PLV	54	3	7.2	0.5	7.3	0.6	7.37	0.02	338	33	150	14	9	1.0	8
	Controls	56	4	7.6	0.7	7.5	0.5	7.33	0.03	257	20	122	14	9	1.0	8
1 h	SURF	38*	4	19.2*	4.8	6.6	0.4	7.41	0.03	363	27	130	15	9	0.3	8
	SURF-PLV	44‡	4	11.0	3.1	7.6	0.7	7.37	0.02	349	29	152	10	12*	0.9	8
	Controls	57	3	7.3	0.4	7.1	0.6	7.36	0.04	277	25	118	11	8	0.4	8
2 h	SURF	25*‡	3	36.8*	6.7	5.7*	0.3	7.46	0.03	365*	31	136	11	9	0.3	8
	SURF-PLV	28‡	2	23.5*	3.6	8.4†	0.3	7.32	0.02	362	38	152	15	14*	1.7	8
	Controls	52	4	8.0	0.5	8.0	0.8	7.33	0.04	249	17	111	10	9	1.0	8
3 h	SURF	20*‡	2	48.3*‡	6.6	5.7*	0.4	7.48	0.04	324	31	128	16	10	0.3	8
	SURF-PLV	24*‡	2	31.6*‡	3.3	8.4†	0.4	7.34	0.01	331	25	139	12	13*	1.3	8
	Controls	53	5	8.1	0.6	8.5	0.8	7.30	0.04	282	32	126	19	8	0.5	8
4 h	SURF	13*‡	1	64.5*‡	2.6	5.7*	0.3	7.47	0.04	321	28	132	13	9	0.2	8
	SURF-PLV	22*‡	2	34.0‡	3.4	8.5†	0.6	7.34	0.02	308	27	136	16	13*	0.4	8
	Controls	52	3	7.7	0.5	8.2	0.4	7.32	0.03	296	25	131	11	6	0.9	7
5 h	SURF	12*‡	2	64.9*‡	3.7	5.9*	0.5	7.46	0.04	312	28	125	12	9	0.1	8
	SURF-PLV	24‡	3	35.1‡	4.6	9.2†	0.8	7.31	0.03	348	39	146	14	14	1.2	8
	Controls	56	6	7.2	0.7	9.1	0.8	7.29	0.03	278	46	121	3	6	0.4	5
6 h	SURF	12*‡	2	61.2*‡	4.7	7.0	1.0	7.45	0.04	326	23	133	14	9	0.2	8
	SURF-PLV	26‡	3	30.8†‡	5.0	10.0‡	1.0	7.29	0.03	338	38	139	13	15*	0.4	8
	Controls	56	4	7.0	0.4	9.9‡	0.7	7.27	0.03	291	57	137	19	7	0.5	4

Gas exchange

Surfactant alone improved Pa_{O_2} from 8.1 (0.7) kPa after onset of ALI to 61.2 (4.7) kPa after 6 h of treatment (P<0.05 *vs* controls; Fig. 1, Table 2). The increase of Pa_{O_2} in the SURF-group was greater than the increase in the SURF-PLV-group after 6 h of treatment (P<0.05 *vs* SURF-PLV; Fig. 1, Table 2). In the PLV-SURF-group the increase of Pa_{O_2} from 7.2 (0.5) kPa after onset of ALI to 30.8 (5.0) kPa after 6 h of treatment was greater than in controls (P<0.05 *vs* controls; Fig. 1, Table 2).

In the SURF group $\dot{Q}s/\dot{Q}t$ decreased significantly compared with controls (51 (5)% at onset of ALI to 12 (2)% 6 h after treatment, P<0.05 *vs* controls; Fig. 2, Table 2). In the SURF-PLV-group $\dot{Q}s/\dot{Q}t$ was significantly decreased compared with controls (54 (4)% at onset of ALI to 26 (3)% after 6 h of treatment, P<0.05 *vs* controls; Fig. 2, Table 2).

Haemodynamics

There were no significant changes between groups in HR, MABP, and SVR. In the SURF-group the MPAP increased from 25 (1) mm Hg at onset of ALI to 30 (3) mm Hg after 6 h of treatment, and was significantly less than in controls and in the SURF-PLV-group (P<0.05 *vs* controls and *vs* SURF-PLV; Fig. 3, Table 1). In the SURF-group, PVR increased significantly from 266 (49) dyn s cm^{-5} at onset of ALI to 560 (83) dyn s cm^{-5} at 6 h of treatment (P<0.05 *vs* ALI-values; Table 1). In the SURF-PLV-group, PVR increased significantly from 268 (28) to 659 (82) dyn s cm^{-5} (P<0.05 *vs* ALI-values, Table 1). In the SURF-group and in the SURF-PLV-group, CO decreased significantly during the treatment period compared with ALI-values (P<0.05 *vs* ALI-values; Table 1). In controls there were no significant changes in PVR and CO.

Lung mechanics

After induction of ALI, static compliance of the respiratory system decreased from 22 (2) ml cm H_2O^{-1} in all groups to 9 (1) ml cm H_2O^{-1}. No further changes of C_{RS} occurred in the SURF-group. In the SURF-PLV-group, C_{RS} improved significantly compared with controls from 9 (1) to 15 (0.4) ml cm H_2O^{-1} at 6 h of treatment (P<0.05 *vs* controls; Fig. 4, Table 2).

Lung injury

The non-dependent lobes in the SURF-group had a significantly smaller injury score for interstitial oedema and emphysema compared with controls and the SURF-PLV-

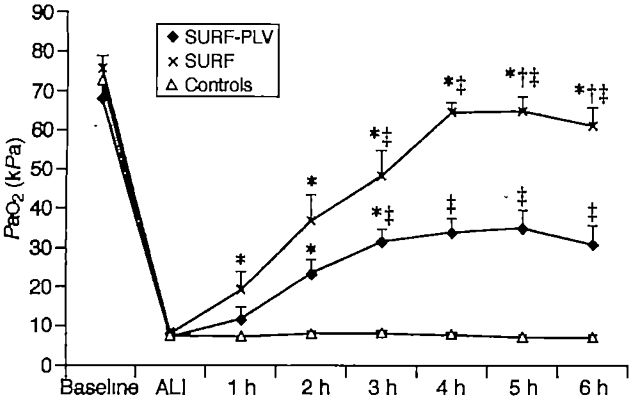

Fig 1 Time course of arterial oxygen tension (Pa_{O_2}) during baseline (pre-lavage), after induction of ALI (post-lavage), and for 6 h thereafter, in controls (*n*=8 at ALI; four pigs died before 6 h after ALI), in pigs treated with surfactant (Curosurf®) after induction of ALI (SURF-group) (*n*=8 pigs, none died), and in pigs treated with surfactant (Curosurf®) followed by PLV with 30 ml kg^{-1} of perfluorocarbon (PF 5080) after induction of ALI (SURF-PLV-group) (*n*=8 pigs, none died). Data are mean (SEM). *Intergroup comparison*: controls *vs* SURF-PLV-group and controls *vs* SURF-group: $^*P<0.05$, and SURF-PLV-group *vs* SURF-group $†P<0.05$ (Kruskal–Wallis ANOVA and post hoc Dunn's test). *Intragroup comparison*: data measured after induction of ALI *vs* data obtained at hourly intervals thereafter $‡P<0.05$ (Friedman test and post hoc Dunn's test).

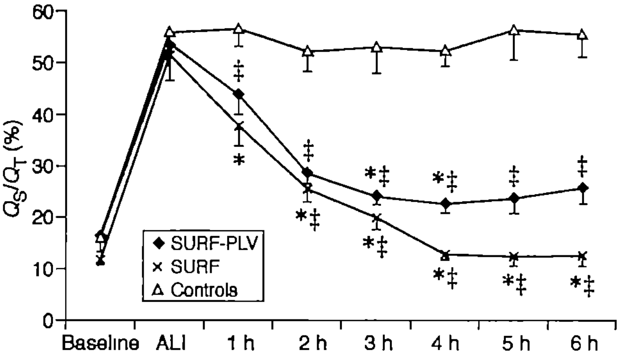

Fig 2 Time course of intrapulmonary shunting (Q_S/Q_T) during baseline (pre-lavage), after induction of ALI (post-lavage), and for 6 h thereafter, in controls (*n*=8 at ALI; four pigs died before 6 h after ALI), in pigs treated with surfactant (Curosurf®) after induction of ALI (SURF-group) (*n*=8 pigs, none died), and in pigs treated with a single surfactant (Curosurf®) followed by PLV with 30 ml kg^{-1} of perfluorocarbon (PF 5080) after induction of ALI (SURF-PLV-group) (*n*=8 pigs, none died). Data are mean (SEM). *Intergroup comparison*. controls *vs* SURF-PLV-group and controls *vs* SURF-group: $^*P<0.05$, and SURF-PLV-group *vs* SURF-group: $†P<0.05$ (Kruskal–Wallis ANOVA and post hoc Dunn's test) *Intragroup comparison*: data measured after induction of ALI *vs* data obtained at hourly intervals thereafter $‡P<0.05$ (Friedman test and post hoc Dunn's test)

group ($P<0.05$, Table 3). In the SURF-PLV-group, scores for interstitial oedema were significantly greater compared with controls in the non-dependent lobes ($P<0.05$, Table 3). Comparing tissue damage in dependent lobes, the SURF-group had significantly less atelectasis and emphysema than controls ($P<0.05$) and less interstitial oedema and emphysema than the SURF-PLV-group ($P<0.05$, Table 3). In the SURF-PLV-group, interstitial infiltration and atelectasis of the dependent lobes was less than in controls and the SURF-group ($P<0.05$ *vs* controls and *vs* SURF), while interstitial oedema and emphysema in the dependent lobes in the SURF-PLV-group was greater than in controls and the SURF-group ($P<0.05$, Table 3).

The overall lung injury score of the SURF-group was less in the non-dependent lobes, compared with the SURF-PLV-group and controls ($P<0.05$, Table 3).

Survival

All animals in both treatment groups survived to the end of the study. In the control-group, four animals died of irreversible hypoxaemia during the study, one after 3 h, two after 4 h, and one 5 h after induction of ALI (Table 2).

Discussion

In this study, we compared the effects of a single, small dose of surfactant alone and combined with a full dose of PLV on oxygenation, haemodynamics, respiratory mechanics, and lung injury in an animal model of ALI. A small dose of surfactant was better than a combined treatment with a small dose of surfactant and PLV to restore gas exchange. Respiratory mechanics were only improved in the group treated with the combination of surfactant and PLV. Atelectasis, interstitial oedema, and emphysema were significantly less in the surfactant group than in controls. Compared with the group receiving surfactant and PLV, the surfactant group had a significant smaller total lung injury score.

Surfactant therapy combined with PLV has been studied in different types of ALI.[19 29] Studies have been done in surfactant deficient pre-term animals,[19 24 26 29] isolated lungs of pre-term animals,[23 27] newborn animals with ALI induced by surfactant wash-out,[21 25 27] and experimental ALI in adult animals.[20 22] Criteria for onset of ALI after surfactant wash-out was a $Pa_{O_2}/F_{I_{O_2}}$ ratio below 8 kPa (60 mm Hg), with the exception of the studies by Hartog and co-workers and Kelly and co-workers, who used a value below 13 kPa (100 mm Hg) to indicate ALI.[20 22] The duration of $Pa_{O_2}/F_{I_{O_2}}$ less than 8 kPa of 30 min to indicate the induction of ALI was specified only in one study.[21] Our lavage procedure caused a stable $Pa_{O_2}/F_{I_{O_2}}$ ratio of 7.6 (0.6) kPa (57 (5) mm Hg) for at least 1 h after the last lavage. The severity of the lung injury in our animals resembles surfactant deficient pre-term animals, shown by the high shunt fraction, which was 54 (4)% after lung injury.

Mrozek and co-workers compared four different treatments in newborn piglets, after induction of ALI. One group received 100 mg kg^{-1} surfactant, one group received PFC in a dose equivalent to the functional residual capacity, one group received PFC 30 min after surfactant replacement, and one group received surfactant 30 min after instillation of

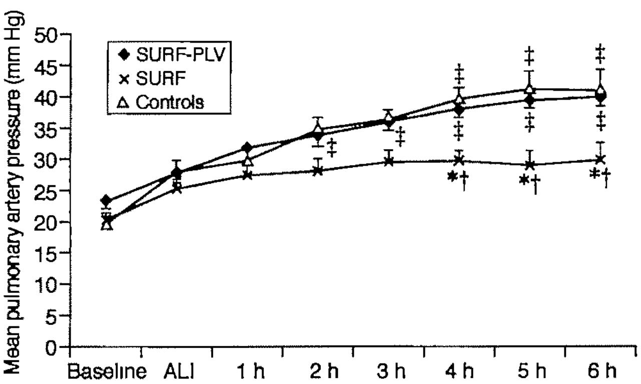

Fig 3 Time course of MPAP during baseline (pre-lavage), after induction of ALI (post-lavage), and for 6 h thereafter, in controls (*n*=8 at ALI; four pigs died before 6 h after ALI), in pigs treated with surfactant (Curosurf®) after induction of ALI (SURF-group) (*n*=8 pigs, none died), and in pigs treated with surfactant (Curosurf®) followed by PLV with 30 ml kg^{-1} of perfluorocarbon (PF 5080) after induction of ALI (SURF-PLV-group) (*n*=8 pigs, none died). Data are mean (SEM) *Intergroup comparison*: controls *vs* SURF-PLV-group and controls *vs* SURF-group: *$P<0.05$, and SURF-PLV-group *vs* SURF-group. †$P<0.05$ (Kruskal-Wallis ANOVA and post hoc Dunn's test) *Intragroup comparison*: data measured after induction of ALI *vs* data obtained at hourly intervals thereafter: ‡$P<0.05$ (Friedman test and post hoc Dunn's test)

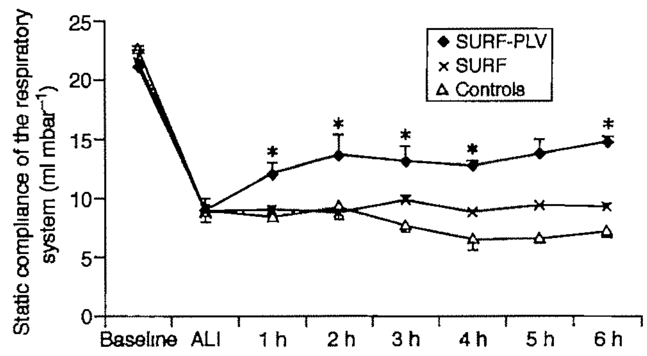

Fig 4 Time course of static compliance of the respiratory system (C_{RS}) during baseline (pre-lavage), after induction of ALI (post-lavage), and for 6 h thereafter, in controls (*n*=8 at ALI; four pigs died before 6 h after ALI), in pigs treated with surfactant (Curosurf®) after induction of ALI (SURF-group) (*n*=8 pigs, none died), and in pigs treated with surfactant (Curosurf®) followed by PLV with 30 ml kg^{-1} of perfluorocarbons (PF 5080) after induction of ALI (SURF-PLV-group) (*n*=8 pigs, none died). Data are mean (SEM). *Intergroup comparison*: controls *vs* SURF-PLV-group: *$P<0.05$ (Kruskal–Wallis ANOVA and post hoc Dunn's test).

PFC.[27] In contrast to our finding that a single dose of surfactant caused the greatest improvement in Pa_{O_2}, Mrozek and colleagues found that a combination of surfactant and PLV was better than the effect of surfactant alone on gas exchange, lung mechanics, and lung pathology. They make no comment on the decrease in Pa_{O_2} after instillation of PFC in the group treated with PLV after surfactant replacement.

These differences could be attributed to the following: (1) different timepoints of measurement, (2) the use of a bovine surfactant (Survanta), (3) a higher dose of surfactant (100 mg kg^{-1}), (4) newborn piglets as study subjects, and (5) the use of pre-oxygenated perflubron (LiquiVent). Another difference was positioning the animals while filling the lungs with PFC, which might have allowed greater perfluorocarbon dose and a more homogenous distribution of PFC throughout the lungs, although this technique appears to be impractical under clinical circumstances. In a study of ALI induced in premature lambs, Leach and co-workers compared either surfactant replacement, a combination of surfactant replacement and PLV, or PLV alone.[29] In this study, a very small dose (5 mg kg^{-1}) of an artificial surfactant (Exosurf) did not improve oxygenation and respiratory mechanics when compared with conventional ventilation. The combination of surfactant and PLV was not better than PLV alone. Leach and co-workers attributed the lack of surfactant efficacy to the small dose used and to the modest physiologic activity of synthetic surfactant, which gives a greater surface tension than natural surfactant.[29]

In our study, improvements in oxygenation and intrapulmonary right-to-left shunt were delayed in the SURF-PLV-group. This could have been because: (1) PLV was started 30 min after surfactant was instilled, to avoid wash-out of exogenous surfactant; (2) inhomogeneous surfactant distribution could have caused PFC to only enter some regions and, thereby, limit alveolar recruitment. Leach and co-workers describe a transient increase in the expiratory resistance of their surfactant-PLV group and suggested that the distal movement of perfluorocarbons could have been delayed, as surfactant will remain in small airways and alveolar ducts.[27]

In a study from Göthberg and co-workers using a model of premature ALI, the treatment of PLV combined with conventional ventilation or combined with high-frequency oscillatory ventilation (HFOV) 2 h after giving 100 mg kg^{-1} of surfactant (Infasurf) improved oxygenation compared with treatment with surfactant and conventional ventilation alone.[17] HFOV after surfactant replacement improved Pa_{O_2} to a similar extent than HFOV combined with PLV and was significantly more effective than PLV and conventional ventilation. The different results of a treatment with PLV and conventional ventilation after surfactant replacement, compared with our data, might be because of different models, a different PFC, a later application of PFC, and different doses of surfactant. Improvement in oxygenation with HFOV, with and without PLV, could be explained by changes in airway pressures and the development of a high intrinsic PEEP from the ventilatory pattern. Previous studies showed that combining PFC and high levels of PEEP enhances the effects of PLV on pulmonary gas exchange.[15–17]

The improvement in C_{RS} in our piglets treated with the combination of surfactant and PLV supports the findings of other investigators, and appears to be dose dependent.[9 13 20] We measured the static compliance of the respiratory system, with an inspiratory shutter technique, to exclude

Table 3 Lung injury score of the non-dependent and the dependent lobes for atelectasis, interstitial infiltration, interstitial oedema, emphysema, and total lung injury score in controls (n=8 at ALI; four pigs died before 6 h after ALI), in pigs treated with a single intratracheal dose of 50 mg kg^{-1} of surfactant (Curosurf®) after induction of ALI (SURF-group) (n=8 pigs, none died), and in pigs treated with a single intratracheal dose of 50 mg kg^{-1} of surfactant (Curosurf®) followed by PLV with 30 ml kg^{-1} of perfluorocarbon (PF 5080) after induction of ALI (SURF-PLV-group) (n=8 pigs, none died). Data are mean (SEM) *Intergroup comparison*: controls *vs* SURF-PLV-group and controls *vs* SURF-group: *P<0.05, and SURF-PLV-group *vs* SURF-group: †P<0.05 (Kruskal–Wallis ANOVA and post hoc Dunn's test). *Intragroup comparison*: non-dependent *vs* dependent lobes. §P<0.05 (Friedman test and post hoc Dunn's test)

	Non-dependent lobes						**Dependent lobes**					
	SURF		**PFC-SURF**		**Controls**		**SURF**		**PFC-SURF**		**Controls**	
	Mean	SEM	**Mean**	SEM	**Mean**	SEM	**Mean**	SEM	**Mean**	SEM	**Mean**	SEM
Atelectasis	0.68*	0.09	0.94*§	0.1	0.3§	0.04	0.78*	0.07	0.08*†	0.03	1.41	0.07
Interstitial infiltration	1.38	0.1	0.31*†	0.08	1.46§	0.02	1.65	0.04	0.34*†	0.04	1.76	0.04
Interstitial oedema	0.1*§	0.04	1.32*†§	0.09	0.5§	0.05	1.11	0.05	2.13*†	0.05	1.2	0.05
Emphysema	0.11*	0.03	1.76†§	0.15	1.9§	0.04	0.19*	0.03	1.47*†	0.05	0.4	0.5
Total injury score	2.27*§		4.33†		3.86		4.02		3.73		3.77	

effects of PFC vapour-pressure on expiratory volumes. We used 30 ml kg^{-1} of perfluorocarbon, approximately the functional residual capacity of healthy lungs and added further liquid according to our past observations.[33] Tütüncü and co-workers compared the effects of PLV with 18 ml kg^{-1} PFC with PLV using 18 ml kg^{-1} saline, in a similar model of ALI in rabbits, and found that compliance of the respiratory system increased in the PFC group.[13] Studying adult rabbits with induced ALI, Kelly and colleagues compared the effects of different treatments.[20] The treatments were PLV with 20 ml kg^{-1} PFC, nebulized PFC, 100 mg kg^{-1} artificial surfactant (ALEC), 100 mg kg^{-1} porcine surfactant (Curosurf®), the combination of PLV and ALEC, the combination of PLV and Curosurf®, and a control group. Our observations support their findings for arterial oxygenation. Regarding lung mechanics, 100 mg kg^{-1} of Curosurf® improved compliance as effectively as the combination of PLV and Curosurf®. In our study, the smaller dose of exogenous surfactant, was not sufficient to improve lung mechanics. Kelly and co-workers point out that surfactant from animals contains surfactant apoproteins, which prevent inhibition of surfactant by protein-rich fluid in lungs after induction of ALI, and that this effect is dose-dependent.[20] In studies in humans, lung compliance decreases after surfactant treatment, despite increases in functional residual capacity and improvements in oxygenation. This could be because of slow recruitment of atelectatic lung areas, with stabilization of the initially opened lung units.[34 35] Lack of improvement in lung compliance after surfactant administration in experimental ALI was also found by Mrozek and co-workers.[27] We consider that the small dose of surfactant used in our study did not entirely overcome surfactant inhibition, and that the amount of lung tissue opened up in the SURF-group, although sufficient to improve gas exchange, was not sufficient to produce effects on C_{RS}.

Treatment with surfactant alone caused less histological injury, for interstitial oedema, atelectasis, and emphysema compared with controls and compared with the SURF-PLV-group. Comparing the overall lung injury scores between groups, treatment with surfactant alone caused less damage in non-dependent lobes compared with controls and the SURF-PLV-group. A small dose of surfactant reduces the inflammatory response in ALI, prevents further atelectasis, and improves gas exchange. The effects on inflammation could be attributed to the apoproteins of natural surfactant, which might prevent inflammation. The greater lung injury scores in the SURF-PLV-group contrasts with previous results of Mrozek and co-workers, who found least injury with the combined treatment.[27] They suggest that the lower inspiratory pressures needed for effective alveolar ventilation could be the reason for less lung injury in this group. The different PFC used for PLV and a higher dose of surfactant could account for these differences. In rats with lavage-induced ALI, Hartog and colleagues compared lung injury after treatment with surfactant, PLV, and high values of PEEP *vs* healthy controls and injured controls.[22] Surfactant prevented progression of lung injury, when compared with healthy controls, and PLV increased lung tissue injury compared with healthy controls.

In our study, we found that cardiac output decreased significantly during the study in both treatment groups, which has not been reported previously in short term studies of lavage-induced lung injury.[26 36 37] However, D_{O_2} and $\dot{V}_{O_2}$ remained unchanged in both groups, indicating maintenance of a sufficient oxygen delivery. A possible explanation for the lower values of CO might be reduced sympathetic activity in both treatment groups because of better oxygenation. This view is supported by poorer survival in control animals. As suggested by Dantzker and co-workers, a reduction in CO could reduce the intrapulmonary right-to-left shunt.[38] The magnitude of this mechanism of shunt reduction with a CO reduction of 40% in the SURF-group and 30% in the SURF-PLV-group, suggests that this would only partly account for the reduction found, and indicate other mechanisms, such as alveolar recruitment, could be involved.

The increase in MPAP in animals treated with the combination of surfactant and PLV could be caused by the PFC. In a study from Morris and co-workers healthy pigs had their lungs filled with 40 ml kg^{-1} of perfluorocarbons and were conventionally ventilated.[35] Pulmonary blood flow was diverted from the dependent regions of the lung, associated with an increase in MPAP. The authors suggested that a greater hydrostatic pressure gradient in PFC-filled alveoli, compared with the gradient in the blood vessels, could cause this effect.[37]

In conclusion, using an experimental model of ALI in piglets, we found that treatment with a single small dose of surfactant improved oxygenation, decreased intrapulmonary right-to-left shunt, and reduced lung tissue damage more effectively than a combination of surfactant with PLV. However, only the combined treatment of exogenous surfactant and PLV improved lung mechanics. Taken with other evidence, these findings show that further research is needed to find the least dose of surfactant that is effective.

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Viscosity and density of common anaesthetic gases: implications for flow measurements

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Although viscosity (μ) is a crucial factor in measurements of flow with a pneumotachograph, and density (ρ) also plays a role in the presence of turbulent flow, these material constants are not available for the volatile anaesthetic agents commonly administered in clinical practice. Thus, we determined experimentally μ and ρ of pure volatile anaesthetic agents. Input impedance of a rigid-wall polyethylene tube (Zt) was measured when the tube was filled with various mixtures of carrier gases (air, 100% oxygen, 50% oxygen+50% nitrogen) to which different concentrations of volatile anaesthetic inhalation agents (halothane, isoflurane, sevoflurane, and desflurane) had been added. μ and ρ were calculated from real and imaginary portions of Zt, respectively, using the appropriate physical equations. Multiple linear regression was applied to estimate μ and ρ of pure volatile agents. Viscosity values of pure volatile agents were markedly lower than those for oxygen or nitrogen. Clinically applied concentrations, however, did not markedly affect the viscosity of the gas mixture (maximum of 3.5% decrease in μ for 2 MAC desflurane). In contrast, all of the volatile agents significantly affected ρ even at routinely used concentrations. Our results suggest that the composition of the carrier gas has a greater impact on viscosity than the amount and nature of the volatile anaesthetic agent whereas density is more influenced by volatile agent concentrations. Thus, the need for a correction factor in flow measurements with a pneumotachograph depends far more on the carrier gas than the concentration of volatile agent administered, although the latter may play a role in particular experimental or clinical settings.

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The pneumotachograph is the most common device used for flow measurements in respiratory mechanics. Flow measurement via a pneumotachograph is based on the principle of detecting differential pressure across a resistive element within the device. Under laminar flow conditions, the differential pressure (also called the pressure drop) is proportional to flow and also to gas viscosity (μ). Changes in μ, therefore, affect the flow rate measured with a resistive-type pneumotachograph.[1 2] The density of a gas (ρ) also affects flow measurements under turbulent flow conditions[3] or when the flow is estimated by using rotating vane flowmeters. Additionally, pressure measurement with laterally positioned pressure transducers is affected by the gas density via the Bernoulli phenomenon.[4]

Although the viscosities and densities of carrier gases (air, oxygen, and nitrous oxide) can be extracted from physical tables,[5] and the density data for the volatile anaesthetic agents can be calculated based on their molecular structure, the viscosity values for carrier gases containing different concentrations of vaporized volatile anaesthetic agents are not available and cannot be readily deduced from theoretical physical equations. Consequently, it is not known how the commonly used volatile inhalation agents in different concentrations affect flow measurements with a resistive-type pneumotachograph. The aim of the present study was, therefore, to determine experimentally whether the different concentrations of clinically administered volatile anaesthetic agents affect the viscosities and

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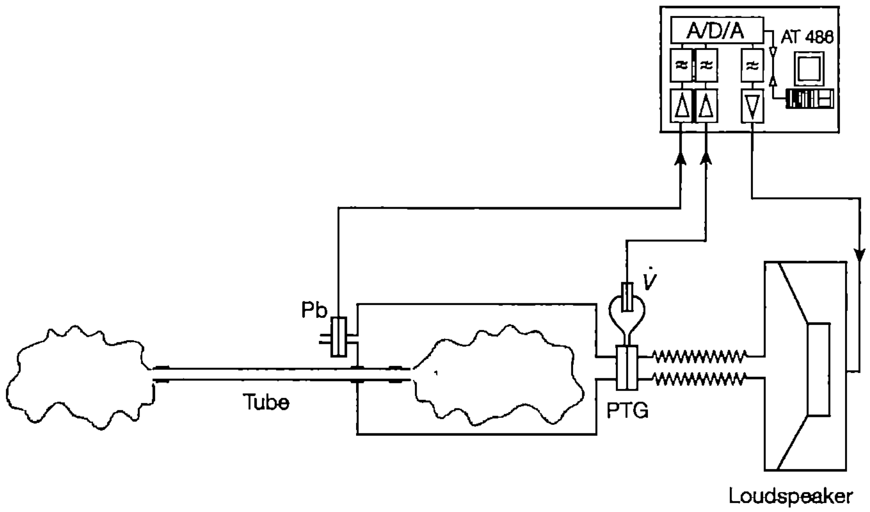

Fig 1 The measurement set-up. *P*b, box pressure; PTG, pneumotachograph; $\dot{V}$ box flow.

densities of the gas mixtures commonly applied in anaesthetic respiratory management, and hence to estimate the extent to which the amounts of the various components affect flow measurements with a pneumotachograph.

Methods

Measurement principle

To determine anaesthetic gases' viscosities and densities, we measured the input impedance of a rigid-wall polyethylene tube (Zt) when the tube was filled with the different gas mixtures. As Zt can be regarded as a frequency-independent resistance and inertance in series, the real part of Zt reflects the resistance of the tube, while the imaginary part (or reactance, *X*) that increases linearly with frequency can be attributed to the inertive effect of the gas ($X=j\omega I$, where ω is the angular frequency, *I* is the inertance and *j* is the imaginary unit $\sqrt{-1}$). At low frequencies, for which the Poiseuille law is still valid, the real part of Zt (resistance, *R*) is linearly related to the viscosity of the resident gas in the tube ($R=8\mu l/r^4\pi$, where *l* and *r* are the length and the radius of the tube, respectively). Furthermore, there is a linear relationship between the imaginary part of Zt and the density of the gas in the tube ($X=n\omega\rho l/A$, where ω is the angular frequency, and *A* is the cross-sectional area of the tube, and *n* is 4/3 in case of parabolic velocity profile and 1 if the velocity profile is blunt).[6] Accordingly, both μ and ρ of any gas in a tube with known geometry can be determined experimentally by measuring Zt.

Measurement apparatus

We adopted the experimental method of Lutchen and colleagues to measure Zt.[7] This technique allowed us to determine Zt in a wide frequency range in order to ensure the validity of the Poiseuille law, while it also permitted us to change the resident gas in the tube. The scheme of the measurement set-up is presented in Figure 1. A loudspeaker-in-box system generated a small-amplitude pseudorandom forcing signal in a rigid-walled plexiglass box (V_{box}=1.6 litre). The oscillatory signal contained seven frequency components in the range 0.117–6.04 Hz. The components in the forcing signal were selected according to the non-sum-non-difference rule[8] to minimize the effects of non-linearities and harmonics cross-talk. In particular, the 2nd, 5th, 11th, 19th, 31st, 59th, and 103rd harmonics of the fundamental frequency (0.0586 Hz) were included in the signal with component amplitudes decreasing with increasing frequency. A rigid polyethylene plastic tube (*l*=29 cm, *r*=1 mm) was led through the front panel of the box, and two similar-sized plastic bags were attached to the internal and external ends of the tube. As the bags were always flaccid, for example, the pressure in the bags was atmospheric, their influence on the impedance measurement could be neglected.

The input flow of the box ($\dot{V}$) was measured with a screen pneumotachograph connected to an ICS 33NA002D differential pressure transducer. The box pressure (*P*b) with reference to the atmosphere was detected with an identical pressure transducer. Signals of *P*b and $\dot{V}$ were 25 Hz low-pass filtered and sampled at 120 s^{-1} with a 12-bit analogue-to-digital board of an IBM-compatible computer.

Procedure

All measurements were performed in the same climate-controlled laboratory under constant atmospheric conditions (970 hPa), with stable temperature (23°C) and humidity. Before each oscillatory measurement, the two bags were emptied by exposing them to direct vacuum until complete collapse. At the beginning of the experiment, the impedance of the box-tube system (Zc) was measured when the plastic bags and the tube were filled with air. Both plastic bags and the tube were then filled with different concentrations of various anaesthetic inhalation agents in turn (halothane, isoflurane, sevoflurane, and desflurane) in 100% oxygen, in a mixture of 50% oxygen+50% nitrogen, or in a mixture of 21% oxygen+79% nitrogen (air). The concentration of the volatile agents were varied between 0.75 and 4% for halothane, 1.25 and 5.4% for isoflurane, 2 and 9% for sevoflurane and 6 and 18% for desflurane by measuring four different concentrations of each within these ranges for each volatile gas. The highest concentrations were limited by the physical characteristics of the vaporizers. Gas mixtures were generated from an anaesthetic machine by the flow of 6 litres of carrier gas through the vaporizer; the outlet was sampled at a rate of 200 ml min^{-1} by means of a Datex AS3 monitor until a steady-state measurement was achieved. Both plastic bags and the tube were then filled with the resulting mixture via a 3-way tap. Before oscillatory measurements, the concentration of each component in the blended gas in the bags was analysed with a Datex AS3 monitor, which was calibrated before each use. Four sets of measurements were made on each gas mixture, the four resulting curves were averaged and used for further analyses (see below). Following a set of measurements with each gas mixture, the external end of the tube was plugged, and the impedance of the closed box (Zb) was determined.

Data analysis and statistics

Fast Fourier transformation was used to compute Zc ($Pb/\dot{V}$ with the tube open) and Zb ($Pb/\dot{V}$ with the tube closed) from the 30-s long recordings by using a 17-s time window and 95% overlapping. As Zc consists of Zb and Zt in parallel, Zt was calculated by parallel removal of Zb from Zc: $Zt = ZbZc/(Zb - Zc)$.

Our data analysis assumes that density and viscosity of a gas mixture change linearly with the density and viscosity values of the pure component gases. Linearity of density necessarily applies to mixtures of ideal gases and it can be assumed that deviations from linearity do not play a significant role in estimating the viscosity. Therefore, multiple linear regression analysis was used to estimate the viscosity and density values of the pure component gases by considering either viscosity or density values of the gas mixtures as dependent, and the amount of component gases as independent variables. Uncertainties in the parameter estimates were expressed as SE values.

Results

Representative input impedance data

The real and imaginary parts of the tube impedance determined experimentally when the system was filled with air or 100% oxygen are presented in Figure 2. The measured real parts for both gases were frequency-independent in the applied range, whereas the reactances increased linearly with increasing frequency.

Viscosity and density of the pure component gases

Viscosity and density values of the pure component anaesthetic gases are demonstrated in Tables 1 and 2, respectively. The viscosity values for pure volatile agents are generally lower than those for the carrier gases. Conversely, markedly greater density values were obtained for the volatile agents than those for the carrier gases.

Viscosity and density of commonly used gas mixtures

Viscosity and density values for gas mixtures commonly used in anaesthetic practice are summarized in Tables 3 and 4, respectively. Clinically applied concentrations of volatile agents have relatively small, although systematic, effects on the viscosity values of the gas mixtures with maximal decrease in viscosity of 3.3–3.5% at 2 MAC desflurane. However, density values of the common anaesthetic gas mixtures were markedly influenced by the volatile agents with maximal elevation in density of 47.5% at 2 MAC desflurane in air. The large changes with desflurane arise from the high concentrations of 1 and 2 MAC for that agent, not from unusually deviant values of viscosity and density.

Discussion

Viscosity and density of the gases commonly used in anaesthetic practice were determined in the present study. We demonstrated that the viscosity values of the common volatile agents are markedly lower than those of the carrier gases routinely applied in anaesthetic management. As in clinical practice the volatile agents are administered in very low concentrations, their net effects on the viscosity, and hence, on the flow measurement with a pneumotachograph do not exceed 4% for routinely used anaesthetic gas mixtures. The density of common anaesthetic gas mixtures was markedly influenced by the presence of volatile agents even at clinically applied concentrations with a possible increase in density of almost 50%.

Methodological issues

Before discussing the implications of the present findings, as concerns the measurement of respiratory mechanics, some methodological issues need to be considered. First, the parameter estimations assume that the measurements were made in the presence of laminar flow in the tube.[6] To verify this assumption, we calculated the Reynolds number ($Re = r v \rho / \mu$) from our experiments, by calculating the axial velocity (v) from the measurements of flow on entry into the plastic box. This calculation revealed that the Reynolds numbers were lower (130–140) than the critical value

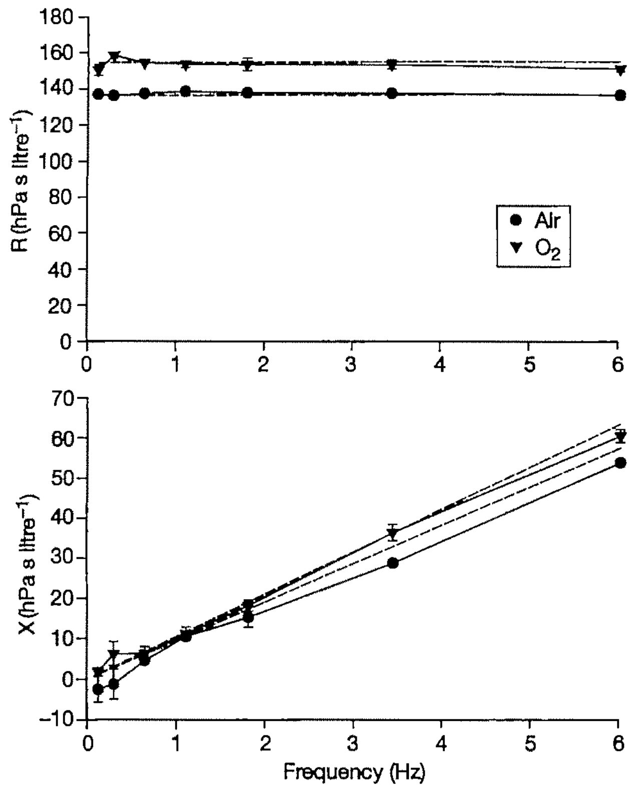

Fig. 2 Resistance (R) and reactance (X) values for air and oxygen (the dashed lines indicate the calculated resistance and reactance values, and the continuous lines represent the resistance and reactance values measured with the present set-up) Error bars represent SD

(1160). Thus, it can be concluded that laminar flow developed in the tube, and thus, the use of the Poiseuille equation to estimate viscosity was appropriate.

Second, on the basis of physical principles, R for a rigid tube increases with increasing oscillatory frequency.[10] Thus, if this phenomenon exerts a significant effect, we should overestimate the viscosity, as the Poiseuille law is valid for low frequencies. In this study, the real part was always almost entirely frequency-independent (e.g. Fig. 2). Therefore, averaging the R values over the frequency range studied did not seem to introduce any systematic error in the estimation of viscosity. Additionally, the I of a rigid tube decreases slightly with increasing oscillatory frequency.[10] In this study, we observed an almost perfect linear increase in X in the frequency range studied. Thus, the inertance can also be considered frequency-independent in our measurements and can be used to estimate the density of the resident gas mixture in the tube.

Validity and accuracy

As the analysis applied in the present study provides viscosity and density values for carrier gases (pure oxygen and nitrogen), comparing our values to those in reference tables[9] (the latter being corrected to temperature of 23°C and atmospheric pressure of 970 hPa) gives information regarding the reliability of the technique used in the present study. Viscosity values for oxygen and nitrogen determined experimentally in the present study are very close to their reference values (differences are 1.7 and 0.9%, respectively) suggesting that viscosity values of other pure component gases are also likely to be reliable. However, density values are slightly underestimated for both nitrogen and oxygen (6.7 and 1.5%, respectively). This small underestimation is most likely because of the slight distortion of the parabolic velocity profile, particularly at the entrance and at the exit of the tube, which decreases the factor 'n' from 4/3 towards 1 in the equation relating inertance to density[6] (see above). Accordingly, a 1–7% underestimation can be expected in all density values reported in the present study.

The precision of estimates for oxygen and nitrogen is excellent in the present experiment with standard errors lower than 2%. Nevertheless, our estimates for the viscosity and density values of volatile inhalation agents display lower accuracy. In the present study, the concentration of volatile agents delivered was limited to the physical capacities of the vaporizers. Thus, extrapolation of the physical parameters for pure volatile gases was based on measurements when these agents were present only at very low concentrations. Indeed, the accuracy of our estimate increased markedly with increasing volatile agent concentration in the carrier gas, with lowest accuracy for halothane (maximum concentration 4%) and highest for desflurane (maximum concentration 18%).

Implications

Flow measurement is sensitive to the viscosity of the gas, as the pressure drop across the resistive element of a pneumotachograph (either screen or Fleisch) is linearly related to this parameter.[3] Thus, a decrease in gas viscosity underestimates the real flow and overestimates the resistance and the elastance, and vice versa. Accordingly, without applying a correction factor, this phenomenon biases the results of studies on respiratory mechanics. In recent publications, following a change in the nature of the inhaled gas, no correction factor was applied to flow measurements, which may have biased their results to some extent.[11 12]

In the present study, as expected, the viscosity of the carrier gas increased significantly when the oxygen content increased. Therefore, calibrating a pneumotachograph with air and using a different carrier gas with high oxygen content will lead to an underestimation of respiratory mechanical parameters. However, for a given carrier gas, the presence of a volatile agent in low concentration is not likely to significantly affect the resulting viscosity. Thus, our results suggest that the effect of the viscosity alteration as a result of volatile agent administration may not be physiologically significant (approximately 4% at most) when a single reading of a respiratory mechanical parameter is made in a given clinical setting. However, when repeated measurements are performed in animal studies or under clinical circumstances in order to compare different agents or populations, it may be important to take into account viscosity changes in the different gas mixtures in the evaluation of respiratory mechanics under different experimental conditions.[13] Given that we determined viscosity values of pure volatile agents, the impact of the altered viscosity on flow measurement can be estimated and in future studies the importance of applying a correction factor will depend on the particular experimental condition.

The density of the gas mixture was affected by the amount of both oxygen and the volatile agents (Table 4).

Table 1 Viscosity of commonly used anaesthetic gases. Numbers between brackets: reference values (9) All values are given at temperature of 23°C and atmospheric pressure of 970 hPa

	Mean (Pa s×10^{-5})	**SE of estimate**
Nitrogen	1 812 (1.781)	0.0082
Oxygen	1.999 (2.018)	0 0073
Halothane	1.249	0.3529
Isoflurane	0 892	0.2439
Sevoflurane	1.276	0.1688
Desflurane	1.452	0.0706

Table 2 Density of commonly used anaesthetic gases at temperature of 23°C and atmospheric pressure of 970 hPa Numbers between brackets. reference values (ρ_{ref}) transformed to 23°C and 970 hPa ($\rho_{ref}=\rho_0\ P_mT_0/P_0T_m$, where P_m=970 hPa, T_0=273 K, P_0=1010 hPa, T_m=300 K and ρ_0=1 429 kg/m^3 for oxygen and ρ_0=1 25055 kg/m^3 for nitrogen) (9)

0	**Mean (kg m^{-3})**	**SE of estimate**
Nitrogen	1 02 (1.093)	0 017
Oxygen	1 23 (1 249)	0.015
Halothane	6 48	0 72
Isoflurane	5 19	0 50
Sevoflurane	6.12	0 34
Desflurane	5 44	0.14

Although the density of the gas in the lungs does not play a very significant role under most experimental conditions, this physical parameter may influence the measured mechanical parameters via the Bernoulli effect in lateral pressure measurements[4] and/or in the event of turbulent flow.[6 14] It may be noted that, as the measurement of flow with a pneumotachograph is based on the detection of a differential pressure between the two ports, the influence of density via the Bernoulli effect is cancelled out in such differential pressure measurements.[3] However, the measurement of pressure at an airway opening is more likely to be affected by the Bernoulli effect and thus by density. Furthermore, density affects flow measurements under conditions of turbulence, when the Reynolds number exceeds a critical value.[14] In this regard, Bates and colleagues[4] proposed an experimental method for determination of the correction factor to be applied at high Reynolds numbers. Our measurements suggest the need for such a correction if either the oxygen content or the volatile agent concentration of the intrathoracic gas is changed during the experimental procedure.

In conclusion, we adopted a measurement technique[7] to determine the physical properties of volatile agents commonly administered in anaesthetic management. The measurements were validated by comparing viscosity and density values of oxygen and nitrogen to their reference values.[9] We conclude that volatile agents in commonly used clinical concentrations slightly affect the gas mixture viscosity. However, the oxygen content in the carrier gas and the nature of the volatile anaesthetic agent affect the density of the gas mixture significantly. Therefore, our results suggest that attention should be paid to the compositions of the commonly used inhalation anaesthetic gases during respiratory mechanical measurements; application of a gas-dependent correction factor may be necessary for accurate flow measurements with a resistive-type pneumotachograph.

Table 3 Viscosity values (Pa s×10^{-5}) of common anaesthetic gas mixtures. Numbers between brackets: relative change in the viscosity because of administration of the volatile agents. The MAC values for halothane, isoflurane, sevoflurane, and desflurane are 0 75, 1 15, 2, and 7.25%, respectively

	Halothane		**Isoflurane**		**Sevoflurane**		**Desflurane**	
	1 MAC	**2 MAC**	**1 MAC**	**2 MAC**	**1 MAC**	**2 MAC**	**1 MAC**	**2 MAC**
100% oxygen	1.9934 (99 7)	1.9878 (99 4)	1.9862 (99 3)	1 9735 (98 7)	1 9809 (99 0)	1 9629 (98.1)	1 9662 (98 3)	1.9334 (96 7)
Air	1 8457 (99 7)	1.8401 (99 4)	1 8385 (99.3)	1 8258 (98 6)	1.8332 (99 0)	1 8152 (98.1)	1.8185 (98.2)	1 7857 (96 5)
50% oxygen	1 8999 (99.7)	1.8943 (99.4)	1 8927 (99.3)	1.8800 (98.7)	1 8874 (99.1)	1.8694 (98 1)	1.8727 (98.3)	1.8399 (96 6)

Table 4 Density values (kg/m^3) of common anaesthetic gas mixtures Numbers between brackets· relative change in the density because of the administration of the volatile agents The MAC values for halothane, isoflurane, sevoflurane, and desflurane are 0.75, 1 15, 2, and 7.25%, respectively

	Halothane		**Isoflurane**		**Sevoflurane**		**Desflurane**	
	1 MAC	**2 MAC**	**1 MAC**	**2 MAC**	**1 MAC**	**2 MAC**	**1 MAC**	**2 MAC**
100% oxygen	1.273 (103 2)	1.312 (106 4)	1.279 (103 7)	1.325 (107 4)	1.356 (109 9)	1.478 (119.8)	1 486 (120.5)	1.739 (141.0)
Air	1 104 (103.7)	1 143 (107 4)	1.110 (104.3)	1.156 (108 6)	1.187 (111 5)	1.309 (123 0)	1.317 (123.7)	1.570 (147 5)
50% oxygen	1 166 (103.5)	1 205 (107.0)	1 172 (104.0)	1 218 (108.1)	1.249 (110.9)	1 371 (121.7)	1.379 (122.4)	1.632 (144.9)

Acknowledgements

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BJA

REVIEW ARTICLE

Minimizing perioperative adverse events in the elderly†

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Elderly patients still have the highest postoperative mortality and morbidity rate in the adult surgical population. Preoperative clinical assessment to detect patients at high risk of post-operative events, and specific intraoperative and postoperative anaesthesia management are important to minimize postoperative adverse events in the elderly.

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Keywords: anaesthesia; complications; age factors, surgery

Among the steadily increasing population of surgical patients aged 65 yr and older, the fastest growing sector is individuals of 85 yr or older.[149] As a result, greater numbers of patients are presenting for surgery with ageing-related, pre-existing conditions that place them at greater risk of an adverse outcome, such as cardiac or pulmonary disease or diabetes mellitus.[122] It is, therefore, not surprising that the elderly have the highest mortality rate in the adult surgical population.[108] Postoperative adverse effects on the cardiac, pulmonary, cerebral systems, and on cognitive function are the main concerns for elderly surgical patients who are at high risk. Recently some studies have focused on elderly surgical patients regarding the incidence of postoperative complications, predictors for developing postoperative complications, preoperative assessment and screening for elderly patients at high risk, and perioperative management. In this review, we document the incidence of postoperative adverse outcomes and discuss ways of improving peri-operative anaesthesia care for this vulnerable surgical population.

Anaesthesia- and surgery-related mortality

Incidence

Mortality associated with anaesthesia and surgery is defined as the death rate within 30 days of operation. Advances in anaesthetic/surgical technique and perioperative care have substantially reduced related mortality.[43 108] However, overall mortality in the general population remains at 1.2%,[108] compared with 2.2% in patients aged 60–69 yr,[108] 2.9% in those 70–79 yr,[108] 5.8–6.2% in patients over 80 yr,[43] and 8.4% in those over 90 yr.[69] Major surgery further increases elderly mortality; for example, emergency abdominal surgery results in a 9.7% mortality for patients over 80 yr,[79] thoracotomy in a 17% mortality for those over 70 yr,[20] and any major surgical procedure a 19.8% mortality in those over 90 yr.[2]

Predictive factors

The function capacity of organs reduces with ageing, resulting in decreased reserve and ability to endure stress.[75 114] Advanced age is, therefore, a significant risk factor for increased mortality.[43 108 114] Co-existing disease further depresses organ function and/or reserve, exacerbating risk.[75 108] For example, pre-existing hypertension, diabetes mellitus, or renal failure contributes to a higher incidence of perioperative myocardial infarction (MI) (5.1%), cardiac death (5.7%)[68] or ischaemia (12–17.7%).[30] Additional risk factors in the elderly[2 43 69 108] (Table 1) include the need for emergency surgery,[2 69] major surgical procedures, ASA physical status III or IV, and poor nutritional status.

One study of 80-yr-old patients concluded that MI was the leading cause of postoperative death.[43] Pre-existing cardiac disease predisposes substantial perioperative risk.[10 30 71 86 109] Patients with coronary artery disease have a 4.1% incidence of perioperative MI,[7] and a 5.5%

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† This review is accompanied by Editorial II.

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Table 1 Risk factors for postoperative mortality in elderly surgical patients *MET indicates metabolic equivalent

ASA physical status	III and IV
Surgical procedures	Major and/or emergency procedures
Co-existing disease	Cardiac, pulmonary disease, diabetes mellitus, liver, and renal impairment
Functional status	<1–4 MET*
Nutritional status	Poor, albumin <35%, anaemia
Place of residence	Not living with family
Ambulatory status	Bedridden

rate of reinfarction if older than 65 yr (compared with 3.5–4.2% rate of reinfarction in the general population).[129] Ischaemic episodes reportedly occur in 24–41% of patients with coronary artery disease during the first week after major non-cardiac surgery.[30 95 96] Ischaemic heart disease combined with previous MI produces a higher incidence of postoperative MI in elderly patients than in younger patients with the same conditions.[10 129] In the general elderly population over 60 yr, the incidence of MI after non-cardiac surgery is reported to be 0.1–0.15%,[108 109] with mortality as high as 50–83%.[109] Tables 2 and 3 list the clinical predictors of increased perioperative cardiovascular risk[47] and the cardiac risk stratification index for non-cardiac surgical procedures,[47] respectively, for the general population.

The respiratory mortality ranged from 0–0.6% depending on the surgical sites and the presence of pulmonary risk factors.[18 105 134] Aspiration during anaesthesia had a high mortality of 5%.[105] The mortality of pulmonary embolism was reported from 0.03–0.64% in elderly patients who underwent incontinence surgery and total hip replacement surgery respectively.[5 133] Risk factors for developing pulmonary embolism include age, malignancy, obesity, and the type of surgery performed.[5 6 127 133] Recent studies demonstrated that prophylactic low dose aspirin or low dose low molecular weight heparin in high risk elderly surgical patients are effective and safe to prevent or decrease the morbidity or mortality of deep venous thrombosis (DVT) and pulmonary embolism.[5 6 127] Neuraxial block can reduce the odds of pulmonary embolism by 55% and deep vein thrombosis by 44%.[120] The Pulmonary Embolism Prevention Trial Collaborative Group recently reported that aspirin reduced the morbidity and mortality of DVT and pulmonary embolism by 30% with a slight increase in gastrointestinal bleeding of lesser severity in elderly patients undergoing surgery for hip fracture.[5]

The cerebrovascular mortality was 0.05% in elderly patients who underwent incontinence surgery. Perioperatively, the period of greatest risk appears to be the postoperative period.[108] It is the most physiologically stressful, with major changes in adrenergic activity, body temperature, pulmonary function, fluid balance, and perception of pain.[95] These changes cause tachycardia and hypertension, increase imbalance in oxygen supply and demand, and incur cardiac ischaemia.[96 109] Most of the pulmonary emboli occurred during the surgical procedure or within 7 days of surgery.[127]

Table 2 Clinical predictors of increased perioperative cardiovascular risk. ECG indicates electrocardiogram *The American College of Cardiology National Database Library defines recent MI as greater that 7 days but less than or equal to 1 month (30 days). †May include 'stable' angina in patients who are unusually sedentary ‡From reference 25 reproduced with permission. From reference 47 reproduced with permission

Major
Unstable coronary syndromes
●Recent myocardial infarction* with evidence of important ischaemic risk by clinical symptoms or non-invasive study
●Unstable or severe angina† (Canadian Class III or IV)‡
Decompensated congestive heart failure
Significant arrhythmias
●High-grade atrioventricular block
●Symptomatic ventricular arrhythmias in the presence of underlying heart disease
●Supraventricular arrhythmias with uncontrolled ventricular rate
Severe valvular desease
Intermediate
Mild angina pectoris (Canadian Class I or II)
Prior myocardial infarction by history or pathological Q waves
Compensated or prior congestive heart failure
Diabetes mellitus
Minor
Advanced age
Abnormal ECG (left ventricular hypertrophy, left bundle branch block, ST–T abnormalities)
Rhythm other than sinus (e g. atrial fibrillation)
Low functional capacity (e.g inability to climb one flight of stairs with bag of groceries)
History of stroke
Uncontrolled systemic hypertension

Accordingly, to decrease perioperative risk in the elderly population requires rigorous preoperative assessment of organ function and reserve, good intraoperative control of concomitant disorders such as coronary artery disease, ischaemic heart disease, hypertension, chronic obstructive pulmonary disease (COPD) or diabetes mellitus, and vigilant postoperative monitoring and pain management. For example, patient-controlled analgesia/epidural analgesia (PCA/PCEA) can decrease postoperative myocardial ischaemia.[15 124]

Postoperative cardiac complications

Physiological changes, incidence rate, and predictive factors

Ageing affects cardiac function in many ways. Stiffening of large arteries increases afterload on the heart, while myocardial stiffening impairs early diastolic filling.[53 114] The beta-adrenergic responsiveness of the heart decreases. Contractility does not change (despite prolongation in duration[26]), but the resulting increase in end-diastolic volume plays an important role in preserving maximal cardiac output during exercise. Conduction abnormalities and bradyarrhythmias are more prevalent in the elderly and hypertension is common, potentially contributing to ischaemic heart disease and sudden cardiac death.

Table 3 Cardiac risk stratification for non-cardiac surgical procedures Risk=combined incidence of cardiac death and non-fatal myocardial infarction †Patients in this group do not generally require further preoperative cardiac testing From reference 47 reproduced with permission

High risk (reported cardiac risk often more that 5%)
Emergency major operations, particularly in the elderly
Aortic and other major vascular surgery
Peripheral vascular surgery
Anticipated prolonged surgical procedures associated with large fluid shifts or blood loss
Intermediate risk (reported cardiac risk generally less than 5%)
Carotid endarterectomy
Head and neck surgery
Intraperitoneal and intrathoracic surgery
Orthopaedic surgery
Prostate surgery
Low risk (reported cardiac risk often more that 1%)†
Endoscopic procedure
Superfical procedure
Cataract removal
Breast surgery

Table 4 Anaesthesia management for elderly patients undergoing major surgery

Preoperative assessment for identifying high risk patients
Careful history
Physical examination
Twelve-lead ECG
Functional status assessment
Nutrition assessment
Preoperative preparation
Effective control of co-existing disease
Stopped smoking for 8 weeks
Training in cough and lung expansion techniques
Chest physiotherapy for elderly at risk of postoperative pulmonary complications
Correct of malnutrition
Routine precautions for major surgery
Temperature monitor and control
Ripple mattress
DVT prophylaxis
Intra-arterial pressure monitoring
Haemodynamic stability
Combination of anaesthetic and vasopressor, beta-blockers or vasodilators
Avoid fluid overload
Quick recovery from anaesthesia
Use short-acting anaesthetic agents
Combine epidural anaesthesia and GA for major abdominal and thoracic surgery
Antagonize neuromuscular blocking drugs
Postoperative period
Prevent hypoxaemia
Supplemental oxygen, reversal of neuromuscular blocking drugs
Prevent hypothermia
Keep warm perioperatively
Effective postoperative pain control
Multimodal analgesia

Antihypertensive treatment appears to reduce cardiovascular mortality and heart failure.[148]

Silent ischaemia and unrecognized MI also occur.[70 153] Elderly patients at high risk for these conditions can be identified preoperatively by ambulatory electrocardiography and/or exercise or pharmacological stress testing.[70 110 153]

The most common cardiac complications associated with surgery in elderly patients are MI and myocardial ischaemia. Infarction usually occurs during the first 3 days after surgery, particularly on the first postoperative day. Most postoperative MIs are silent and have non-Q wave characteristics.[109 129] Postoperative pain control combined with residual anaesthetic effects is responsible for the silent nature of an MI, making them difficult to detect and their precise onset difficult to determine.[7 10 86 109 129] Monitoring for specific ECG changes (S–T elevation and Q wave) accompanied by elevated CK, CK-MB isoenzyme and troponin T and I levels enables diagnosis. These data also permit identification of an MI as definite, probable or possible.[10 30] Measurement of troponin T and I is replacing the use of CK, CK-MB levels to detect minor and early cardiac cell damage because of the greater sensitivity and specificity of these markers, especially in patients undergoing non-cardiac surgery with skeletal muscle injury, and those with chronic renal disease.[3] Combined with measurement of myoglobin levels or detection of prolonged ST–T change, troponin levels can be an accurate indicator allowing early detection of high risk of postoperative MI.[3] The specificity of cardiac troponin I for detection of MI (99%) was significantly different from that of MB creatine kinase (81%) (P<0.005).[3]

Patients at high risk of myocardial ischaemia should be monitored intraoperatively and for 3 days postoperatively for ST segment depression, a specific marker of ischaemic morbidity.[72] As with MI, troponin levels are a more sensitive and earlier indicator of myocardial ischaemia than CK levels or ST–T wave change,[10] and should be measured in patients who are at high risk or demonstrate ECG or haemodynamic evidence of cardiovascular dysfunction.[10]

Perioperative management

The principles underlying perioperative anaesthetic management of elderly surgical patients are provided in Table 4.

Preoperative cardiac assessment

Many tools are available for preoperative cardiac evaluation. Preoperative assessment of cardiac functional capacity via the estimated energy requirements for various activities (Table 5) often is adequate to identify elderly patients with good exercise tolerance.[4 47] Goldman's cardiac risk profile (Tables 6 and 7) can be used to predict morbidity/mortality in patients undergoing non-cardiac surgery.[62] For elderly patients with documented or suspected coronary artery disease, Potyk has developed a relatively easy stepwise guide that integrates patient risk into anaesthetic and surgical management strategies (Fig. 1).[113]

Clinical markers of active coronary disease can be ascertained from a careful history and functional capacity

Table 5 Estimated energy requirement for various activities. MET indicates metabolic equivalent. From reference 47 reproduced with permission

1 MET	Can you take care of yourself?
	Eat, dress, or use the toilet?
	Walk indoors around the house?
	Walk a block or two on level ground at 2–3 m.p.h or 3.2–4.8 km h^{-1}?
	Do light work around the house like dusting or washing dishes?
4 METs	Climb a flight of stairs or walk up a hill?
	Walk on level ground at 4 m.p.h or 6.4 km h^{-1}?
	Run a short distance?
	Do heavy work around the house like scrubbing floors or lifting, or moving heavy furniture?
	Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?
>10 METs	Participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?

Table 6 Cardiac risk index. From reference 62 reproduced with permission

Risk category	**Points**
Aged >70 yr	5
Myocardial infarction within last 6 months	10
S_3 gallop or jugular venous distension	11
Significant valvular stenosis	3
Rhythm other than sinus or premature atrial contractions	7
Premature ventricular contractions >5/min	7
Poor general medical condition	3
Abdominal or thoracic aorta surgery	3
Emergency surgery	4
Total	53

Table 7 Goldman multifactorial risk assessment. From reference 62 reproduced with permission

Risk class	**Points**	**Risk**	
		Complication (%)	**Mortality (%)**
I	0–5	0.7	0.2
II	6–12	5.0	2.0
III	13–25	11	2.0
IV	>26	22	56

assessment, and then used to evaluate the level of risk and guide preoperative cardiac testing. For example, patients with minor clinical predictors appear to have low risk for coronary stenosis.[110 153] Similarly, assessment using the American College of Cardiologists (ACC)/American Heart Association (AHA) Guidelines based on clinical markers, before coronary evaluation and treatment, cardiac functional capacity, and type of surgery dramatically decreases the number of preoperative cardiac tests performed.[47] Clinical assessment using these guidelines also has been shown to reduce the costs of preoperative evaluation and to improve cardiac outcome in vascular surgery patients.[15]

Twelve-lead ECG is a screening test for all elderly patients. Left ventricular hypertrophy or ST segment depression less than 0.5 mm are independent factors associated with adverse cardiac events during major vascular surgery.[86] Clinically stable elderly patients undergoing low or intermediate risk surgical procedures usually require no further preoperative testing other than 12-lead ECG.[153] Ambulatory ECG can be used to identify patients with arrhythmias and silent ischaemic episodes,[47] but the use of these data to predict perioperative cardiac events remains controversial.[29 70]

The use of advanced cardiac tests to evaluate risk should be considered primarily when anaesthetic and surgical management are likely to depend on test results. For example, conduction abnormalities and supraventricular and ventricular arrhythmias are not uncommon in elderly patients,[62] and the underlying cardiac disease must be investigated before surgical treatment. In patients with second-degree (Mobiz II) or third-degree (complete) atrioventricular block, insertion of a temporary or permanent pacemaker will be necessary before elective surgery.[47] Patients with cardiac murmurs should be referred for echocardiographic examination before elective surgery to detect aortic stenosis or regurgitation or mitral stenosis, common conditions in the elderly population.[47] Symptomatic or severe aortic stenosis must be treated by aortic valve replacement before non-cardiac major surgery.[47] Patients with aortic regurgitation should receive some form of preoperative prophylaxis for endocarditis.[47] Preoperative dobutamine stress echocardiography (DTS) or radianuclide ventriculography (RVG) screening for vascular surgical patients at high risk is unnecessary.[68 126]

Clinically unstable elderly patients with ischaemic heart disease or severe coronary artery stenosis placing them at high risk of perioperative MI should be referred for angiography and prophylactic coronary revascularization[126] before undergoing high risk surgery. Indications for coronary angiography are defined by the ACC/AHA.[47]

Exercise stress testing provides an objective measure of functional capacity and information about preoperative myocardial ischaemia or cardiac arrhythmias. It is recommended by the ACC/AHA as the first non-invasive test for ambulatory patients.[47] For patients at intermediate risk scheduled for elective high risk surgical procedures such as major vascular surgery, the decision to perform exercise stress testing depends on the patient's functional status, and the risk associated with the specific procedure. Patients aged 65 yr or older who are able to perform at least 2 min of supine bicycle exercise, raising the heart rate above 99 beats min^{-1}, are at low risk for perioperative cardiac complications.[60] For elderly patients who cannot undergo exercise stress testing because of a bedridden condition, claudication or lower extremity pain,[110] dipyridamole thallium scintigraphy, or dopamine stress echocardiography can provide the essential information.[110] Intermediate-risk patients undergoing surgery with evidence of cardiac ischaemia will require postoperative intensive care and intensive monitoring. Detection of severe cardiac ischaemia mandates

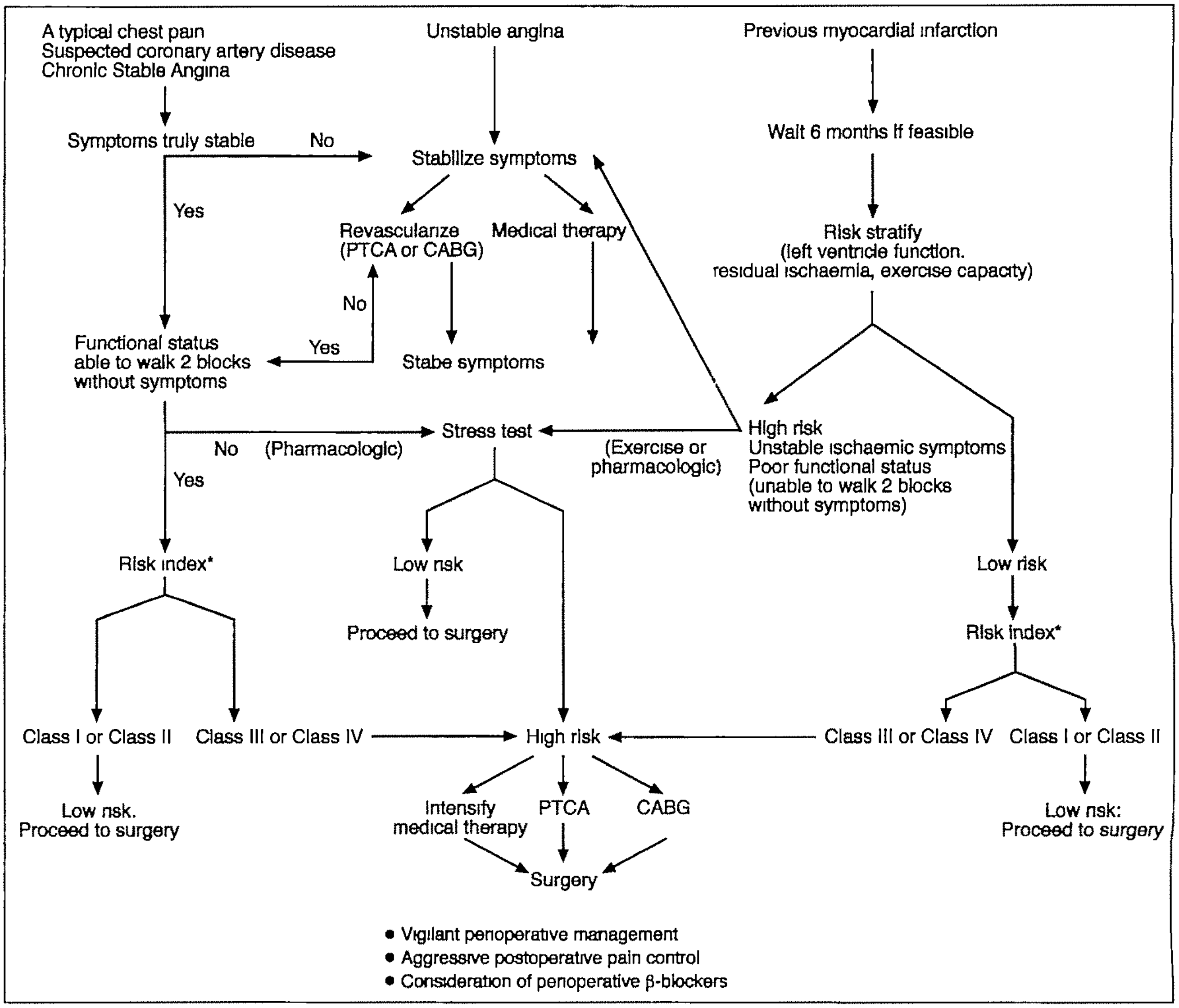

A typical chest pain
Suspected coronary artery disease
Chronic Stable Angina
Unstable angina
Previous myocardial infarction
Symptoms truly stable
No
Stabilize symptoms
Wait 6 months if feasible
Yes
Revascularize (PTCA or CABG)
Medical therapy
Risk stratify (left ventricle function. residual ischaemia, exercise capacity)
No
Yes
Functional status able to walk 2 blocks without symptoms
Stable symptoms
Stress test
No
(Pharmacologic)
(Exercise or pharmacologic)
High risk
Unstable ischaemic symptoms
Poor functional status
(unable to walk 2 blocks without symptoms)
Yes
Risk index*
Low risk
Low risk
Proceed to surgery
Risk index*
Class I or Class II
Class III or Class IV
High risk
Class III or Class IV
Class I or Class II
Low risk. Proceed to surgery
Intensify medical therapy
PTCA
CABG
Low risk: Proceed to surgery
Surgery
• Vigilant perioperative management
• Aggressive postoperative pain control
• Consideration of perioperative β-blockers

Fig 1 Approach to patients with known or suspected coronary artery disease undergoing elective surgery. For all patients undergoing surgery, antianginal medications should be taken with a sip of water on the morning of surgery, aspirin therapy should be discontinued for 7 days; and diuretic therapy should be discontinued on the morning of surgery * indicates preoperative risk indexes described by Goldman *et al* and modified by Detsky *et al* PTCA, percutaneous transluminal coronary angioplasty, CABG, coronary artery bypass grafting. From reference 110, reproduced with permission.

cancellation of surgery or performance of a less invasive elective procedure.

Anaesthetic management

Perioperative anaesthetic management varies according to the needs of the patient and of the surgical procedure. In elderly patients, the overall goals are to provide an appropriate operative environment, preserve myocardial and haemodynamic function, control for the effects of pre-existing disease on surgery, and avoid adverse perioperative events such as myocardial ischaemia or infarction.

General and regional anaesthesia (epidural or spinal) result in comparable short- and long-term cardiac morbidity and mortality in the elderly following peripheral vascular surgery, total hip arthroplasty, or transurethral prostate resection.[32 40 45 48] Thoracic epidural anaesthesia in vascular surgery, coronary artery bypass grafting, and abdominal surgical procedure appears to provide greater benefit than the other techniques: it attenuates the perioperative stress response, improves myocardial oxygenation, reduces the release of troponin T, and effectively controls refractory unstable angina pectoris as a result of sympatholysis.[77 89 104] Some studies also report that epidural anaesthesia decreases blood loss during total hip arthroplasty, prevents intraoperative hypertension in patients with intraoperative ischaemia, and results in a lower incidence of reoperation for inadequate tissue perfusion during vascular surgery.[32 40 120] Perioperative infusion of bupivacaine and fentanyl significantly reduced the amount of perioperative myocardial ischaemia in elderly patients with traumatic hip fracture.[124] Local anaesthesia caused fewer ischaemic episodes than general anaesthesia in high risk elderly patients who underwent cataract surgery.[61] A recent systemic review on 141 trials including 9559 patients reported that overall mortality and the number of MI were reduced by one-third in patients who were allocated to neuraxial block.[120] These advantages strongly support the use of regional anaesthesia and analgesia for elderly patients undergoing surgery.[61 73 120 124]

Maintaining intraoperative and postoperative haemodynamic stability is crucial to ensuring a balance between myocardial oxygen delivery and oxygen demand in the elderly.[48] It is prudent to maintain perioperative heart rate and arterial pressure within 20% of the normal awake value and the haematocrit should be maintained above 30%.[131] Hypertensive patients are prone to wide fluctuations in these parameters during surgery, especially at the induction of anaesthesia and tracheal extubation, because of decreased intravascular fluid volume and baroreflex sensitivity.[107] Hypertension detected on admission to hospital is not uncommon in elderly patients, and elevated systolic arterial pressure (treated or untreated) and untreated mild hypertension on admission are reported to increase the incidence of silent cardiac ischaemia.[70] For example, patients over 70 yr with hypertension and diabetes mellitus undergoing surgery who have intraoperative increases in arterial pressure of more than 20 mm Hg lasting 15 min or more have a higher incidence of postoperative ischaemic cardiac complications than their counterparts.[30] These patients also are likely to display an exaggerated pressor response to tracheal intubation and to require vasodilators to control intraoperative hypertensive episodes.[16]

Antihypertensive therapy should be continued on the day of surgery, with the exception of drugs such as reserpine. Clonidine or a beta-blocking drug should be given preoperatively to patients with mild or moderate hypertension or admission systolic hypertension[107]. In patients over 50 yr old with essential hypertension undergoing intestinal or orthopaedic surgery, perioperative administration of clonidine 6 mg kg^{-1} orally 120 min before anaesthesia and 3 mg kg^{-1} i.v. over the final hour of surgery appears to reduce sympathetic output, increase sensitivity to phenylephrine, and improve circulatory stability.[107] In contrast, perioperative discontinuation of long-term clonidine or beta-blocker therapy can cause rebound hypertension,[47] so should be carefully evaluated. Severe hypertension (e.g. diastolic arterial pressure $\geq$110 mm Hg) should be well controlled before elective surgery after 2 weeks effective antihypertensive therapy.[51]

Long-term beta-blocker therapy is not popular for elderly hypertensive patients with MI because of its limited effectiveness in the presence of diabetes, asthma or heart failure, and unacceptable side effects such as bradycardia, hypotension, cardio-inhibitory and vasopressor carotid sinus syndromes, depression, fatigue, and reduced libido.[83] Perioperatively, the primary side effects of beta-blocker administration are hypotension, bradycardia, and bronchospasm,[145] conditions easily detected by routine perioperative monitoring. Moreover, short-term perioperative use of beta-blocking drugs does not appear to have a harmful effect: in one study of beta-blocker *vs* placebo, the incidence of systemic arterial pressure greater than 80–90 mm Hg and/or heart rate greater than 40 beats min^{-1} was rare and did not differ between the two groups.[145] Therefore, assuming no contraindications, prophylactic beta-blocker therapy may be useful in avoiding adverse cardiac outcome in elderly hypertensive patients undergoing major surgery at intermediate or high risk of a negative outcome.[47] Further randomized controlled trials in elderly patients need to be carried out.

Risk of myocardial ischaemia and mortality can be reduced in patients at high risk of coronary artery disease by administration of atenolol.[145] In two recent prospective randomized studies, atenolol was given intravenously before induction of anaesthesia and every 12 h postoperatively until patients could tolerate oral administration, which continued until postoperative day 7 or the day of discharge, whichever came first. This regimen resulted in a 50% lower incidence of myocardial ischaemia during the first postoperative 48 h, a 40% lower incidence during the first postoperative week, and reduced risk for death at 2 yr.[145]

Risk of perioperative myocardial ischaemia increases in the presence of tachycardia. One study has reported that intraoperative tachycardia resulted in postoperative reinfarction in 14% of patients with previous MI.[129] Continuous perioperative infusion of esmolol appears to be effective in controlling heart rate below the ischaemic threshold, thereby reducing the incidence of postoperative myocardial ischaemia in patients with significant preoperative cardiac ischaemia who are undergoing vascular surgery.[115]

Nitroglycerin also reduces the incidence of myocardial ischaemia.[44] Perioperative use is recommended for patients previously taking nitroglycerin to control ischaemic signs or symptoms or those who develop symptoms of ischaemia postoperatively.[47] Further study is needed to define the use of nitroglycerin in elderly patients who have hypertension with bradycardia.

That intraoperative hypotension is a risk factor for postoperative myocardial ischaemia remains controversial.[10] Preoperative hypertensive patients appear more likely to develop intraoperative hypotension than non-hypertensive patients. In one study, intraoperative hypotension (30% decrease from pre-induction arterial pressure) resulted in perioperative reinfarction in 20% of patients with previous MI.[129] Another study of patients undergoing non-cardiac surgery with hypertension and diabetes mellitus reported ischaemic cardiac complications in 19% of patients who had intraoperative decreases in MAP greater than 20 mm Hg lasting 60 min or more. Decreases greater than 20 mm Hg lasting 5–59 min increased the incidence of postoperative ischaemic cardiac complications.[30] A third study of the incidence of postoperative myocardial infarction in patients with ischaemic heart disease undergoing non-cardiac surgery found no significant difference in intraoperative hypotensive episodes between patients with and without MI.[10] One current study reported that deliberate hypotension to MAP of 45–55 mm Hg induced by epidural anaesthesia was safe for elderly patients over 70 or 50–69 yr with co-existing cardiac disease, hypertension, or diabetes mellitus who underwent total hip replacement. Patients were given supplemental oxygen, continuous haemodynamic monitoring, and sufficient i.v. infusion to avoid hypovolaemia. The postoperative cardiovascular complication rate was 6% and postoperative delirium was 9% in this patient group.[152]

However, it seems prudent to maintain arterial pressure within 20% of the awake value. Efforts should be made to avoid intraoperative hypotension or to shorten the duration of hypotension when it occurs.

Postoperative respiratory complications in elderly patients

Physiological changes, incidence rate, and predictive factors

COPD, pneumonia, and sleep apnoea are common in the elderly. Closing capacity increases with age,[24] and forced expiratory volume in 1 s (FEV_1) declines 8–10% each decade because of decreased compliance of the pulmonary system and of muscle power.[82] Arterial blood oxygen tension decreases progressively with age-induced ventilation/perfusion mismatch, diffusion block, and anatomial shunt.[132]

Postoperatively, pulmonary complications occur in 2.1–10.2% of elderly patients[108] and include pneumonia, hypoxaemia, hypoventilation, and atelectasis, all of which prolong intensive care unit stay and increase elderly mortality. Clinical predictors of adverse pulmonary outcome include the site of surgery, duration and type of anaesthesia, COPD, asthma, preoperative hypersecretion of mucus, and chest deformation.[80 81 100 144] The most significant of these is the site of surgery.[81 144] Obesity and older age are no longer considered risk factors.[130] Chronic smoking within 1 month preoperatively increases risk approximately sixfold.[18]

The most important preoperative assessment instruments remain a detailed history, clinical examination, and evaluation of functional status.[81] The presence of dyspnoea, smoking, coughing, and wheezing should be addressed in the history.[130] Pulmonary function tests such as the ability to climb several flights of stairs can offer as much predictive value as spirometric assessment of pulmonary function.[150] For example, the results can be used to determine whether to cancel a proposed surgery or perform a less invasive procedure conferring less risk, such as laparoscopy, to decrease the likelihood of adverse outcome.[130] Preoperative spirometry is useful in identifying patients at risk for adverse outcome following thoracic or upper abdominal surgery.[130] Emergency, thoracic, and abdominal surgery have the highest pulmonary complication rates.[81 144]

Functional predictors include increased residual volume, and decreased FEV_1 and single-breath transfer factor for carbon monoxide (TL, CO, SB).[13] A decrease in the ratio of FEV_1 tovital capacity (FEV_1/VC) and in Pa_{O_2} are risk factors in patients undergoing vascular surgery.[144] For patients with COPD undergoing bilateral volume reduction surgery, the inability to walk at least 200 m in 6 min before or after pulmonary rehabilitation or a resting room air Pa_{CO_2} $\geq$45 mm Hg result in increased postoperative mortality and prolonged hospital stay (>21 days).[134] Aspiration as a result of significant impariment of protective laryngeal reflexes function can also cause severe postoperative pulmonary deterioration in elderly patients.[105]

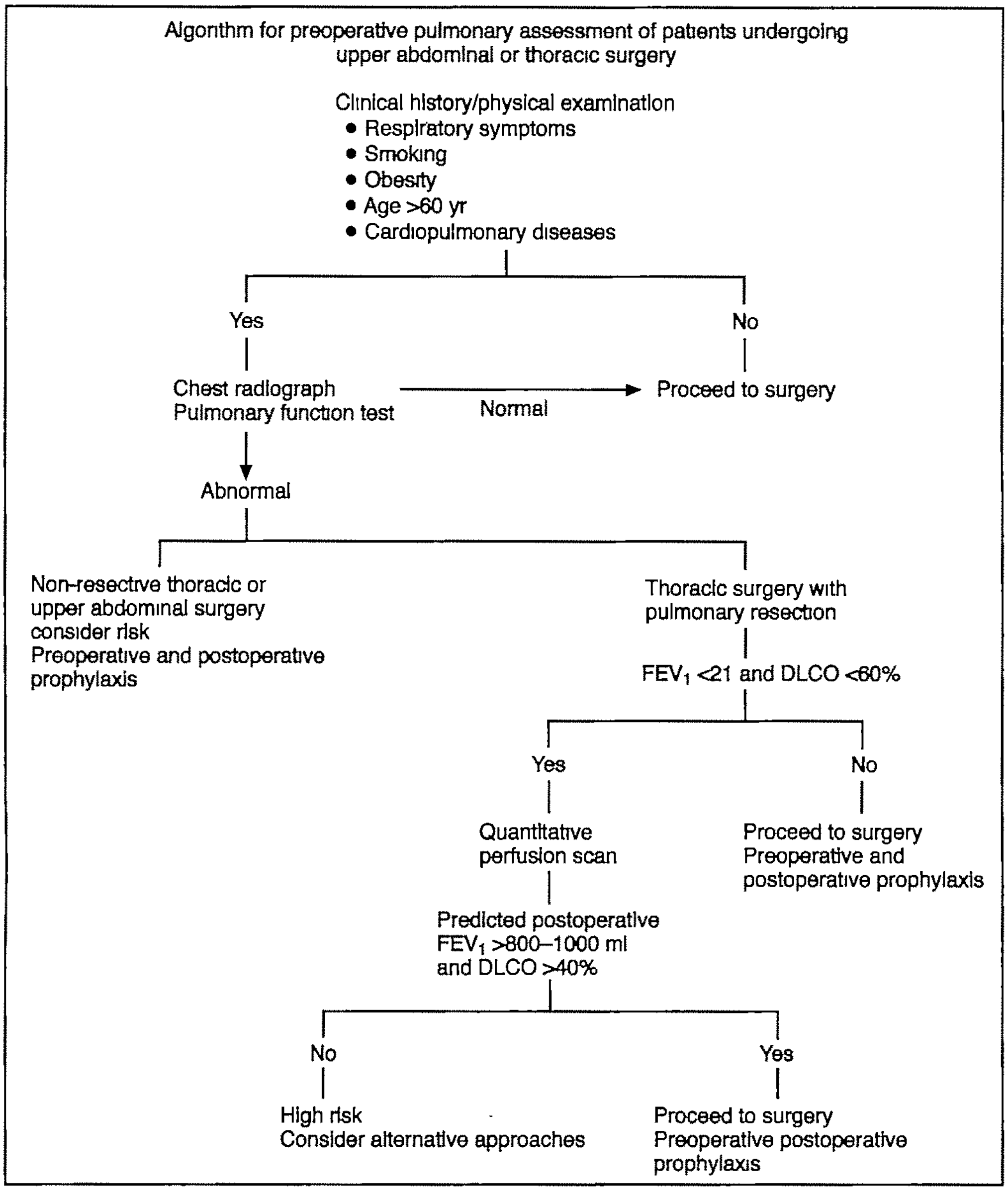
Perioperative management

Preoperative preparation

Patients at high risk of pulmonary complications require some preparation for surgery to minimize risk (Table 4). An algorithm exists for preoperative pulmonary assessment of patients undergoing upper abdominal or thoracic surgery (Fig. 2).[80] Patients who smoke cigarettes should quit at least 8 weeks before surgery to minimize high airway reactivity and risk of bronchospastic obstruction of the airway, mucus trapping, and regional atelectasis.[18 130] High risk elderly patients should be trained in forced cough and lung expansion techniques before surgery, as well as in how to cooperate with the ventilator to avoid discomfort during postoperative ventilation. Patients with COPD should receive preventive therapy with mucolytic and bronchodilating agents.[64] Prophylactic ventilation, however, is ineffective in avoiding pulmonary complications in high risk elderly patients undergoing major, elective abdominal aortic reconstruction.[128] Perioperative chest physical therapy can decrease the incidence of postoperative pulmonary complications,[28] but pulmonary infection should be well controlled before surgery.[64]

Anaesthesia technique

Anaesthesia has profound effects on pulmonary function and gas exchange, resulting in decreased functional reserve capacity (FRC), increased closing volume (CV), and impaired hypoxic pulmonary vasoconstricton (HPV). Regional anaesthesia confers significantly lower risk of postoperative hypoxaemia.[100 120] Regional anaesthesia also is preferred for transurethral resection of the prostate (TURP), because it reduces the risk of pulmonary oedema,


Algorithm for preoperative pulmonary assessment of patients undergoing upper abdominal or thoracic surgery
Clinical history/physical examination
• Respiratory symptoms
• Smoking
• Obesity
• Age >60 yr
• Cardiopulmonary diseases
Yes
No
Chest radiograph
Pulmonary function test
Normal
Proceed to surgery
Abnormal
Non-resective thoracic or upper abdominal surgery consider risk
Preoperative and postoperative prophylaxis
Thoracic surgery with pulmonary resection
FEV1 <2l and DLCO <60%
Yes
No
Quantitative perfusion scan
Proceed to surgery
Preoperative and postoperative prophylaxis
Predicted postoperative FEV1 >800–1000 ml and DLCO >40%
No
Yes
High risk
Consider alternative approaches
Proceed to surgery
Preoperative postoperative prophylaxis

From reference 80. Reproduced with permission

Fig 2 Algorithm for preoperative pulmonary assessment of patients undergoing upper abdominal or thoracic surgery.

decreases blood loss, and permits early detection of any change in mental status.[8] Spinal anaesthesia reduces central venous pressure, potentially resulting in greater absorption of irrigating fluid than general anaesthesia.[59] Epidural analgesia may reduce the incidence of postoperative atelectasis and pulmonary infection,[11 120] and, relative to general anaesthesia, epidural anaesthesia appears to reduce significantly the incidence of postoperative pulmonary complications in 80-yr-old patients.[139] The combination of general anaesthesia and intra- and postoperative epidural analgesia reportedly decreases the incidence of respiratory complications in patients undergoing abdominothoracic oesophagectomy and improves the rate of recovery, as indicated by early extubation and shorter ICU and hospital stay.[21 120] However, avoiding general anaesthesia with tracheal intubation may reduce the risk of postoperative bronchospasm.

Postoperatively, the residual effects of anaesthetic agents, prolonged effects of neuromuscular blocking drugs, and post-surgical pain can contribute to pulmonary complications. Postoperative hypoxaemia is common,[100] as is respiratory depression, which a survey of 198 103 anaesthetics has cited as the most common cause of postoperative death and coma attributable to anaesthesia.[135] Almost all patients surveys received opioid analgesics and neuromuscular blocking drugs for which antagonists were not administered.[135] Similarly, risk of a critical event appears to increase with the combined use of opioid premedication, intraoperative fentanyl greater than 2.0 $\mu g\ kg^{-1}\ h^{-1}$, and neuromuscular blocking drugs.[43] Risk also increases in the presence of residual pancuronium-induced block.[17] Applying these data to elderly patients, it is important to remember that: (1) the perioperative opioid requirement for the elderly is lower than that of younger patients,[50] (2) short-, or intermediate-acting neuromuscular blocking drugs are to be used, and (3) antagonists should be given to reverse residual neuromuscular blocking drugs effects. In addition, supplemental oxygen should be given by facemask during awaking from anaesthesia, transfer to the post-anaesthesia care unit, and for several days postoperatively to prevent late nocturnal hypoxaemia.[121]

Fluid replacement

Perioperative fluid replacement must be managed carefully in elderly patients to prevent the development of postoperative pulmonary oedema as a result of age-related prolonged extracellular water (ECW) expansion. Compared with 5 days for young patients with sepsis, elderly septic patients require 10 days to excrete overexpanded ECW.[31] The elderly also require more prolonged inotropic and ventilatory support.[31] Renal function deteriorates with age with reduction in renal plasma flow, glomerular filtration rate, and altered renal tubular function. The renal ability to balance sodium and water is impaired in elderly patients as a result of low plasma renin activity, urinary and blood aldosterone levels, and decreased response to ADH.[131] Urine output monitoring and pulmonary artery catheterization are more valuable to guide fluid therapy in elderly patients than in young patients[131]. Fluid replacement should be controlled within normal maintenance levels, and vasoconstrictors, inotropic drugs, and small colloid infusions should be used to manage hypotensive episodes in elderly patients with emphysema or those undergoing lobectomy, pneumonectomy, and lung volume reduction procedures.[38] In the presence of cardiac or renal disease, i.v. fluids should be cautiously administered in elderly patients undergoing TURP. To prevent the TURP syndrome, plasma sodium levels must be monitored closely during this procedure. Another method is to regularly measure breath ethanol by irrigating with an ethanol containing glycine solution.

Postoperative cerebrovascular complications

Physiological changes, incidence rate, and predictive factors

Ageing is accompanied by a progressive loss of neurones in the brain and a decline in grey-matter tissue.[156] In addition, neurotransmitter molecules and receptors for dopamine and catecholamines are reduced in number. Vision, hearing, taste, and touch/sensation are compromised.[147] The threshold for pain increases, but this does not alter the need for perioperative analgesia in the elderly because the perceived severity of pain is strongly influenced by intense emotional and psychological factors.[67] Cognitive function declines progressively,[78] and co-existing disease accelerates this process. The autonomic reflex responses for maintaining homeostasis,[37] thermoregulation,[27] laryngeal reflex activity, and overall baroreflex responsiveness are significantly impaired.[111] Regional cerebral blood flow (rCBF) in the parietal, temporo-parietal, and temporal cortex decreases, particularly in the presence of carotid atherosclerosis[35].

Stroke is defined as a focal neurological deficit having a sudden onset and persisting for longer than 24 h. Risk factors for stroke in elderly patients include hypertension, atherosclerosis, physical inactivity, compromised cerebral vessel wall integrity, co-existing cerebrovascular and/or ischaemic heart disease, carotid occlusion, peripheral vascular disease, diabetes mellitus, and intraoperative haemodynamic instability (Table 8).[154] The most prevalent of these is hypertension, control of which can safely and effectively decrease elderly cerebrovascular morbidity and mortality.[14] Most published stroke rates reflect outcome of vascular or coronary artery bypass graft surgery. One recent study of elderly women undergoing surgery to treat incontinence reported a 0.3% cerebrovascular accident rate.[133] The highest incidence of ischaemic stroke appears to be associated with previous cerebrovascular disease, COPD and previous vascular disease (PVD), which confer a thirteenfold, ninefold, and eightfold increase in risk, respectively.[88]

Perioperative management

Preoperative history detailing neurological symptoms and physical examination for carotid bruits should be performed routinely in elderly patients undergoing neurological as well as other major surgical procedures. Preoperative carotid scanning in patients with these symptoms or signs can identify those at high risk for adverse outcome following coronary artery bypass graft surgery and/or vascular surgery.[41] For patients who have carotid bruits, additional testing is essential to detect the severity of the carotid stenosis. The overall principles of anaesthetic management for neurological procedures in the elderly are listed in Table 4.

Carotid endarterectomy may be indicated to prevent stroke in elderly patients who have transient ischaemia or asymptomatic stenosis greater than 60% of the diameter of the internal carotid artery.[12] Although carotid endarterectomy has a higher incidence of stroke than any other non-cardiac surgical procedure,[12 133] elderly patients appear to be able to tolerate carotid endarterectomy without increased risk of postoperative stroke and death.[12] Regional anaesthesia may be preferred for carotid endarterectomy because it permits reliable cerebral monitoring without the use of electroencephalography and results in fewer postoperative complications.[52] However, general anaesthesia facilitates control of arterial blood pressure, ventilation, and oxygenation. In addition, transcranial Doppler monitoring can be

Table 8 Risk factors for postoperative stroke in elderly

Preoperative factors	Pre-existing cerebrovascular disease Ischaemic cardiac disease Atherosclerosis Carotid occlusion Preoperative vascular disease Hypertension Diabetes mellitus Physical inactivity
Intraoperative and postoperative factors	Haemodynamic instability Hypoxaemia

used during general anaesthesia to assess cerebral perfusion, detect intraoperative emboli, and prevent stroke.[58] Cerebral protection during carotid endarterectomy is achieved with the use of hypothermia, barbiturate drugs, and induced hypertension. Perioperative control of systemic arterial pressure also is important because both hypertension and hypotension predispose to neurological morbidity.[154]

Postoperative delirium

Incidence rate and predictive factors

Postoperative delirium is characterized by incoherent thought and speech, disorientation, impaired memory, and attention. The reported incidence of this effect varies from 5.1 to 61.3%,[34,39,65] a wide range likely because of differences in diagnostic criteria, study populations, and methods of observation. Elderly patients usually manifest delirium following a lucid interval of 1 postoperative day or more, a condition known as interval delirium.[34] Symptoms are often worse at night. Alternatively, the condition can be silent and unnoticed, or misdiagnosed as depression.[138] However, the effects of elderly postoperative delirium are evident in increased morbidity, delayed functional recovery, and prolonged hospital stay. Fortunately, the postoperative cognitive dysfunction is a reversible condition in the majority of elderly surgical patients. Only 1% has persistent cognitive dysfunction at 1–2 yr after the surgery.[1]

Preoperative risk factors predisposing to delirium include ageing, lack of education, re-operation, polypharmacy and drug interaction, alcohol and sedative-hypnotic withdrawal, endocrine and metabolic compromise, impaired vision and hearing, sleep deficiency, anxiety, depression, and dementia.[39,76,101,106] Bilateral total knee arthroplasty is associated with a significantly higher incidence of acute delirium than unilateral total knee arthroplasty in patients over 80 yr.[92] Moller's study[101] on 1218 patients over 60 yr who underwent major surgical procedures demonstrated that increasing age and duration of anaesthesia, little education, a second operation, postoperative infections and respiratory complications were risk factors for early postoperative cognitive dysfunction. Only age is a risk factor for late postoperative cognitive dysfunction. Hypoxaemia and hypotension do not appear to be predictors.[101] Intraoperative risk factors include hypoperfusion and microemboli of air or blood cells during cardiac surgery, fat embolism during orthopaedic surgery, severe bilateral loss of vision in ophthalmological patients, and major intraoperative blood loss (haematocrit <30%).[98,106] However, in Moller's study, there was no relation between cognitive dysfunction and blood loss (the amount of blood loss was not reported).[101] Postoperative room change to a quiet, dark and isolated environment also may contribute.[137]

Recent studies did not show that anticholinergic drugs, barbiturate premedication or benzodiazepines are implicated in the development of postoperative delirium.[101,116,151] Preoperative psychoactive agents seemed to be a modifiable risk factor for postoperative delirium.[39] There appears to be no difference in the effects of general, epidural, or spinal anaesthesia on the incidence of postoperative delirium following total knee arthroplasty or TURP procedures.[101,119,151] However, cognitive function appears to be better preserved in elderly patients who undergo TURP with regional anaesthesia without intraoperative sedation.[33] Postoperative patient-controlled epidural analgesia can improve mental status in elderly patients.[97] The use of auditory evoked potentials and the bispectral index to monitor hypnotic status and detect awakening during general anaesthesia can help anaesthetists to adjust the delivery of anaesthetic agents as needed to maintain surgical anaesthesia.[46,57] One recent randomized double-blinded study in elderly hip or knee replacement surgery in our hospital confirmed that bispectral index monitoring, in particular, may decrease anaesthetic requirement during general anaesthesia and facilitate more rapid recovery.[155] However, this study failed to show any difference between cognitive function with or without bispectral index monitoring.[155]

Perioperative management

The principles of prevention are listed in Table 9. Preoperative assessment of the patient's physical and mental status and documentation of chronic medications are important to recognize and reduce the risk associated with pre-existing sensory or perceptual deficits. A multicomponent intervention strategy aimed at six risk factors—cognitive impairment, sleep deprivation, immobility, visual or hearing impairment, and dehydration—may be effective in preventing postoperative delirium.[74]

As no specific risk factors for cognitive dysfunction have been proven to relate to anaesthetic management and postoperative pain control,[101] early recognition of delirium is important.

Nurses should be well trained in detecting the earliest signs of delirium. Where possible, ambulatory surgery should be encouraged because of its short surgical duration and permitting elderly patients to recover in their familiar home environment. Herniorrhaphy and ophthalmological procedures in elderly patients are being performed in ambulatory surgical units under local and monitored anaesthesia care regimens.[51] The increasing use of laparoscopy will allow more elderly surgical patients to return home on the day of surgery.

Speech, consciousness, perception, orientation, coherence, memory, and motor activity can be assessed preoperatively to determine baseline cognitive status and postoperatively to measure change in function using the Mini Mental State Examination (MMSE) (Table 10), which is reliable, easy to conduct, and useful for serial testing in fluctuating conditions.[54] MMSE should be administered to patients at high risk of postoperative delirium.

Once postoperative confusion has been diagnosed, elderly patients should be managed with extra vigilance. Postoperative complications such as pneumonia, urinary tract infection, electrolyte disorder or fluid imbalances are major reasons for postoperative delirium in elderly patients. After the appropriate cause is identified and treated, the preferred approach for treating delirium is oral administration of haloperidol 0.25–2.0 mg 1–2 h before bedtime. For more agitated patients, haloperidol can be delivered intramuscularly, 0.5 mg per h, until symptoms are adequately controlled. Chlorpromazine also is effective, but can lead to a severe reduction in arterial pressure. Diazepam can be used alone or in combination with other antipsychotic drugs and is especially effective for delirium tremens. Thiamine is the key drug for the management of Korsakoff's psychosis.

If delirium progresses to coma, standard treatment for control of the airway, breathing, and circulation should be instituted. After recovery from an acute episode, a psychiatric or psychosocial referral may aid early functional rehabilitation. Nursing assistance at home will help to rehabilitate patients who are discharged early from hospital. Physiotherapy and occupational therapy also may be important adjuncts to rehabilitation.[106]

Postoperative hypothermia

Perioperative hypothermia is prevalent in both young and elderly surgical patients, but more frequent, pronounced and prolonged in the elderly who have compromised ability to regain normal thermoregulatory control quickly.[142] In the early postoperative period, mild hypothermia can elevate norepinephrine concentrations and increase peripheral vasoconstriction and arterial blood pressure, thereby contributing to cardiovascular ischaemia and arrhythmia.[55] Mild hypothermia may also increase blood loss during total hip replacement procedures[125] and the risk of wound infection,[66] decrease drug metabolism, and prolong hospitalization.[87]

Anaesthetics and ambient temperature contribute to hypothermia.[36] As drug metabolism is impaired[87] and anaesthetic-induced inhibition of thermoregulatory response is more severe than in younger patients,[84] use of the lowest possible effective dosage/concentration of anaesthetic agent in the elderly is important. Whether anaesthesia is general or regional appears to have no effect on the production of perioperative hypothermia.[19]

Maintaining normothermia can reduce the risk of adverse outcome. It has been shown to decrease cardiac morbidity by 55%, and a perioperative core temperature of 36.7 (0.1) *vs* 35.4 (0.1)°C reportedly reduces cardiac morbidity during the early postoperative period.[56] Elderly patients should, therefore, be maintained at normal core body temperature. Intraoperative techniques for maintaining core temperature include the use of warmed cotton blankets, a warmed water mattress, warmed i.v. fluid, heated and humidified inspired gases, and forced air warming. The latter is both effective and safe.[85] The only exception to this recommendation for normothermic control is neurosurgery, where mild hypothermia (34°C) is of benefit because it decreases cerebral metabolism and prevents cerebral ischaemia.[136] Temperature must be returned to normal as soon as possible.

Postoperatively, shivering is not common in elderly patients. However, when it occurs, it increases metabolic rate by 20–38%.[23] Factors contributing to postoperative shivering include intraoperative hypothermia (infusion of cold fluids, inhalation of cold and dry anaesthetic gases, exposure of internal organs, duration of surgery, and age and sex), decreased sympathetic activity, adrenal suppression, uninhibited spinal reflexes, and postoperative pain.[23 102] Although no relationship has been demonstrated between axillary temperature and the occurrence of shivering,[23] postoperative shivering can be treated by skin-surface warming, radiant heat application, or pharmacological approaches.[102] The drugs useful for controlling shivering include methylphenidate, orphenadrine, magnesium sulphate, the opiates (fentanyl, morphine and meperidine), naloxone, clonidine, nefopam, and ketanserin. Meperidine and clonidine are effective for managing both postoperative shivering and postoperative pain.[102]

Postoperative pain management

Postoperative pain increases the risk of adverse outcome in elderly patients by contributing to cardiac ischaemia, tachycardia, hypertension, and hypoxaemia. Effective analgesia can reduce the incidence of myocardial ischaemia and pulmonary complications, accelerate recovery, promote early mobilization, shorten hospital stay, and decrease medical care costs.[11 21 120 124 139] Early mobilization which enhances recovery, prevents DVT and decreases morbidity and mortality in elderly patients, can be achieved by epidural anaesthesia or balanced analgesia.[120 123] However, postoperative pain control often is inadequate in the elderly, because of concerns about drug overdose, adverse response, or risk of opioid addiction. Control is made more difficult by the fact that the expression and perception of pain are affected by changes in the patient's mental status.[50]

Current postoperative analgesic techniques include: sustained-release morphine[63]; non-steroidal anti-inflammatory drugs (NSAIDs); PCA/PCEA;[9] local anaesthetic techniques (neuroaxial,[9] intra-articular,[117] nerve block[118]); and non-pharmacological management (transcutaneous acupoint electrical stimulation).[146] However, few studies of these techniques focus on the analgesic requirements of the elderly. PCA and PCEA are recommended because they permit use of relatively low doses of opioids and result in fewer complications than intramuscular opioids.[49] Epidural analgesia has been recommended after thoracic, abdominal, and major vascular surgical procedures.[38,130] However, the PCA/PCEA technique can be used only in patients who can participate in self-medication, which excludes those with cognitive dysfunction. For patients with dysfunction, pain management must rely on the physician's judgment and measures of vital signs such as arterial pressure, heart rate, respiratory rate, restlessness, and sweating, which are, unfortunately, non-specific for pain control.

Table 9 Prevention of postoperative delirium. From reference 106 reproduced with permission. *MMSE, Digit Symbol Substitution Test †From reference 74 reproduced with permission. ‡From reference 65 reproduced with permission

Preoperative assessment
Detailed history of drugs
Medical problem evaluation
Detection of sensory or perceptual deficits
Detection of cognitive impairment by neuropsychologic testing*
Mental preparation (orientation and communication) before to surgery†
Use of geriatric-anesthesiologic programme‡
Intraoperative precautions
Adequate oxygenation and perfusion
Correct the electrolyte imbalance
Adjust drug dose
Minimize the variety of drugs
Avoid atropine, flurazepam, scopolamine
Postoperative care
Environmental support
Well-lit cheerful room
Quiet surroundings
Keep patient oriented
Visit by friend or family
Pain control
Postoperative intervention (hearing aid, vision aid, non-pharmacological sleep aid, early mobilization, correction of dehydration)†
Identify risk-associated drugs
Anticholinergics
Depressants
H_2-antagonists
Reassure patient and family

The morphine requirement for PCA for elderly patients can be calculated using the following formula:[94] average first 24 h postoperative morphine requirement (mg)=100 − age. The initial bolus and subsequent incremental doses should be low to safeguard elderly patients. Oxygen saturation should be monitored[90] to avoid analgesia-induced hypoxaemia, which is common. To minimize the risk of an opioid-related adverse effect, a balanced analgesic technique combining opioids, non-opioids, and local anaesthetic agents should be used.[118] The combination of opioids and local anaesthetics such as bupivacaine or ropivacaine for PCEA can produce satisfactory analgesia without episodes of either respiratory depression or sustained hypotension.[21,42] Epidural ropivacaine at 0.1–0.2% can provide adequate pain control with less motor block than a higher concentration of bupivacaine 0.175% would induce.[9,22]

Choosing a less invasive surgical procedure, when possible, can decrease postoperative pain in elderly patients. Laparoscopic procedures appear to be an effective alternative. For example, laparoscopic cholecystectomy is safe, and results in minimal pain, a short hospital stay, and quick recovery compared with open cholecystectomy in elderly patients.[91] Laparoscopic herniorrhaphy, nephrectomy and nephroureterectomy for tumour removal, paraoesophageal hernia repair, and laparoscopy-assisted colon resection for carcinoma also are possible in elderly patients.[99,141,143]

Malnutrition

Malnutrition is not unusual in the elderly. A survey of nutrition status in patients over 70 yr indicates that 7% have a lower haemoglobin value, and that 11.4% of elderly men and 16.9% of elderly women have albumin levels less than 35 g litre^{-1}.[93] Severe protein malnutrition also may be present.[112]

Table 10 Mini-mental state exam. From reference 54 reproduced with permission

Maximum score	*Orientation*
5	What is the (yr) (season) (month) (date)(day)? [1 point]
5	Where are we. (state) (country) (town) (hospital) (floor)?
	Registration
3	Name three objects, 1 s to say each. Then ask the patient all three after you have said them. Give 1 point for each correct answer. Then repeat them until he learns all three. Count trials and record.
	Attention and calculation
4	Serial 7's. 1 point for each correct. Stop after five answers. Alternatively spell 'world' backwards
	Recall
3	Ask for the three objects repeated above. Give 1 point for each correct
	Language
9	Name a pencil, and watch (2 points). Repeat the following 'No ifs, ands or buts' [1 point]. Follow a three-stage command: 'Take a paper in your right hand, fold it in half, and put it on the floor' [3 points] Read and obey the following: CLOSE YOUR EYES [1 point]. Write a sentence [1 point] Copy design [1 point]
30	Total score

The risk factors for malnutrition in the elderly include social isolation, limited financial resources, poor dentition, alcohol consumption, weight loss, depression, diarrhoea, constipation or any other chronic medical disease,[103] and polypharmacy.[93] Adverse effects of malnutrition include delayed wound healing, greater risk of sepsis, wound infection, and increased mortality.[103 112 140] Preoperative assessment of nutrition status is, therefore, important for elderly patients. Global assessment should include dietary history and physical and laboratory evaluation. Simplified tools such as the Nutritional Risk Assessment Scale and the Mini Nutritional Assessment should be applied.[103] When malnutrition is detected, intervention in the form of a nutritional supplement is indicated, and related underlying diseases such as anaemia should be treated before the elective surgical procedures.

Obesity is another type of malnutrition in elderly patients who are at increased risk of diabetes mellitus and cardiovascular disease. Anaesthetists should pay more attention in obese patients to: the compromised airway; the risk of decreased intrathoracic volume; and intraoperative head and arm position by the use of padding pillows beneath the head to maintain the cervical spine in the plane of the long axis of the thoracic spine.

Conclusion

Perioperative morbidity and mortality in elderly patients will continue to be an important problem. Preoperative clinical assessment to recognize patients at intermediate or high risk of postoperative events by careful history taking, physical examination, and function capacity assessment is important to guide anaesthesia management and to decrease cost by reducing the number of preoperative cardiac or pulmonary tests. Specific intraoperative and postoperative anaesthesia management in terms of maintenance of haemodynamic stabilization and normothermia, effective postoperative pain control, and prevention of hypoxaemia, will minimize postoperative adverse events in the elderly. To summarize the recommendations for clinical management of the elderly.

1. Preoperative assessment to determine the elderly patients at high risk of postoperative adverse outcome.
2. Preoperative testing (invasive or non-invasive) only when test results are likely to change the proposed surgery or intervention, or to indicate the need for high risk invasive monitoring such as pulmonary artery catheterization.
3. Effective perioperative control of co-existing disease.
4. Maintenance of stable perioperative haemodynamics for all elderly patients using vasopressor or vasodilator drugs, or beta-adrenoceptor block, or a combination of appropriate therapies.
5. Where possible, use of a less invasive surgical procedure, for example laparoscopy on an ambulatory basis.
6. Intensive perioperative monitoring of high risk patients.
7. Prevention of hypoxaemia, hypothermia, and delirium.
8. Effective postoperative pain control.

Incorporating each of these elements into decision making for perioperative management of elderly patients can only benefit outcome in this rapidly growing and increasingly vulnerable surgical population.

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BJA

SHORT COMMUNICATIONS

Neuromuscular monitoring in intensive care patients: milliamperage requirements for supramaximal stimulation†

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We investigated the effects of peripheral oedema on the supramaximal current required for neuromuscular monitoring of critically ill patients. We studied 32 sedated patients who had not needed a neuromuscular blocking drug. The presence of oedema over the volar aspect of both wrists was assessed by a blinded observer and graded (grade 0, no oedema; grade 1, mild oedema; grade 2, gross oedema). The supramaximal current was derived by applying an incrementally increasing current over the ulnar nerve and measuring the amplitude of the electromyographic (EMG) response of the first dorsal interosseous muscle. The supramaximal current was that current above which there was no significant increase in EMG amplitude. It was 40 mA in the absence of oedema. This current was significantly increased in the presence of grade 1 oedema (60 mA, Mann–Whitney test, $P<0.01$) and grade 2 oedema (82.5 mA, Mann–Whitney test, $P<0.01$). In the presence of oedema, the required supramaximal current decreased significantly after the application of pressure over the stimulating electrodes (Wilcoxon signed rank test, $P<0.05$). Supramaximal current in critically ill patients is increased in the presence of peripheral oedema. We recommend that nerve stimulators used for neuromuscular monitoring in the ICU are capable of delivering a stimulus current of at least 100 mA.

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Keywords: intensive care; monitoring, neuromuscular function, supramaximal stimulus; equipment, neuromuscular monitor

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The effects of neuromuscular blocking agents may be more variable in critically ill patients because of changes in their pharmacokinetics and pharmacodynamics. It is important to monitor the effects of these drugs so that paralysis is adequate but excessive doses of drug are avoided.

Neuromuscular monitoring relies on the application of a supramaximal current so that the response of all motor units is assessed. The supramaximal current is the current above which there is no increase in the evoked muscle response. At this stimulus current, all motor units are firing in response to nerve stimulation. A current of 50–60 mA provides supramaximal stimulation in all patients during anaesthesia.[1] Should a supramaximal stimulus not be achieved then the degree of neuromuscular block may be overestimated and subsequent clinical decisions may be inappropriate.

Critically ill patients commonly develop peripheral oedema largely as a result of the development of an increased extracellular fluid volume.[2] Patients may also develop a marked core-periphery temperature gradient as a result of hypoperfusion. These physiological changes might be expected to alter the current required for supramaximal stimulation by increasing the electrical impedance of the tissues. Furthermore, the development of critical illness polyneuropathy may reduce the amplitude of the induced action potentials.[3]

Materials and methods

After obtaining Ethics Committee approval, we studied 32 intensive care patients who were mechanically ventilated. Sedation was standardized using a well-established scoring system based on the Ramsay score. No patient received a neuromuscular blocking agent before or during the period of assessment. Plasma electrolyte concentrations and core-periphery temperature gradient were recorded. A blinded

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observer (N.J.N.H.) graded the presence of oedema on both wrists. Grade 0 indicated no oedema, grade 1 mild oedema, and grade 2 gross oedema. Hand dominance was noted.

Electromyographic (EMG) studies were performed by stimulating the ulnar nerve and recording the EMG amplitude over the first dorsal interosseous muscle. In all cases, the recordings were made using the Dantec Neurostim 2000® electromyograph. The site of stimulation was prepared with acetone and ECG-type electrodes were placed over the ulnar nerve at the wrist. The recording electrode was placed over the first dorsal interosseous muscle. The hand was then thermally insulated. Thumb skin temperature was recorded.

The polarity of the stimulating current applied over the ulnar nerve was consistent; we used a signal with a square waveform and duration of 0.2 ms. In all cases the cathode was distal. The stimulating current was applied in a graded fashion, increasing from 0 to 100 mA in 5 mA increments over approximately a 10 min period. The amplitude of the EMG response was recorded and measured on the display using cursors. The process was then repeated after the application of continuous pressure over the stimulating electrodes. In each patient, measurements were made in both the dominant and the non-dominant hands. The pressure was applied for 15 s before the start of repeat measurements and for the duration of these measurements. The supramaximal stimulus was that current above which there was no significant increase in recorded EMG amplitude despite an increase in current applied.

As our data was categorical and the supramaximal current was greater than the maximum current deliverable by our apparatus in a small number of patients, we applied non-parametric tests to our data, which were analysed using SPSS (Windows 95 version 7). We applied the Mann–Whitney test to compare the supramaximal current between groups. The Wilcoxon signed rank test was used to assess any effect of pressure or hand dominance on the supramaximal current. Spearman's rank correlation and analysis of covariance were applied to assess the effect of core-periphery temperature gradient in the presence of oedema.

In eight patients the grade of oedema was different in each hand, irrespective of hand dominance. The data from each patient were, therefore, not aggregated and the recordings from each hand were analysed separately so that 32 patients yielded 64 sets of data.

The median supramaximal current was 40 mA in non-oedematous limbs. In comparison with the non-oedematous state, the presence of grade 1 oedema was associated with a significantly raised supramaximal current (median 60 mA, $P<0.01$, Mann–Whitney test) and in the presence of grade 2 oedema it was 82.5 mA (median, $P<0.01$, Mann–Whitney test). The application of pressure made no difference to the supramaximal current where there was no oedema, but the supramaximal current decreased significantly to 50 mA in the presence of grade 1 oedema (Wilcoxon signed rank test, $P<0.05$) and to 75 mA in the presence of grade 2 oedema (Wilcoxon signed rank test, $P<0.05$) (Fig. 1). When pressure was not applied, there were five supramaximal current values greater than 100 mA but after the application of pressure all values fell within the 0–100 mA range. Hand dominance did not affect the supramaximal current (Wilcoxon signed rank test). There was no relationship between supramaximal current and the core-periphery temperature gradient ($r=0.2$, $P=0.26$). There was no evidence of an effect of oedema on this relationship (analysis of covariance $P=0.9$).

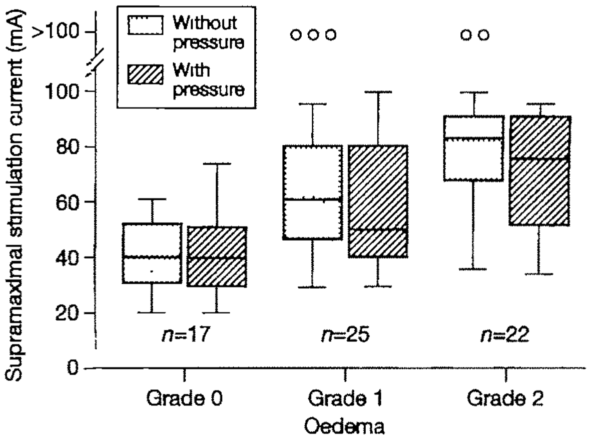

Fig 1 Milliamperage current (mA) required for supramaximal stimulation in critically ill patients with differing grades of peripheral oedema. Median currents supramaximal current are depicted as a horizontal line before the application of pressure (light shading) and after the application of pressure (dark shading). The limits of the box represent the 25th and 75th percentiles and the bars represent the range. Individual patients with current requirements greater than 100 mA are indicated as O The median supramaximal current was 40 mA in non-oedematous limbs In comparison with the non-oedematous state, the supramaximal current in the presence of oedema was significantly raised ($P<0\ 01$, Mann–Whitney test): grade 1 oedema median supramaximal current=60 mA and grade 2 oedema median supramaximal current=82.5 mA. The application of pressure (dark shading) made no difference to the supramaximal current C where there was no oedema, but it decreased significantly (Wilcoxon signed rank test, $P<0.05$) to 50 mA in the presence of grade 1 oedema and to 75 mA in the presence of grade 2 oedema (Wilcoxon signed rank test, $P<0\ 05$).

Comment

The use of neuromuscular blocking drugs in intensive care is common and the incorrect monitoring of neuromuscular function may lead to inappropriate clinical decisions. The ability to monitor neuromuscular function correctly depends upon delivering a supramaximal current at which all muscle fibres respond to the applied stimulus. Failure to deliver this current may make assessment difficult or may lead to an overestimation of the degree of neuromuscular block. In addition, critically ill patients may exhibit altered sensitivity to these agents.[4]

In order to elicit the stimulation of a nerve it is important to deliver an adequate electrical charge. Charge is the product of current intensity (mA) and pulse width (ms). The current intensity generated by a nerve stimulator is directly related to the emitted voltage and inversely related to the impedance ($I=V/R$). It has been demonstrated clinically that in assessing neuromuscular function the ability to deliver this current consistently is related to the pulse width, electrode placement and polarity.[5] In our study, all these factors were consistent. The Dantec Neurostim 2000® electromyograph has the ability to deliver a constant current over a wide range of impedance.

Kopman and Lawson[1] demonstrated that a stimulus of 50–60 mA is required for supramaximal stimulation in a population of anaesthetized patients. In a population of critically ill patients without peripheral oedema we found the same stimulus current was required. However, the presence of oedema increases the current required for supramaximal stimulation. For patients with grade one oedema 60 mA was required and for patients with grade 2 oedema, 82.5 mA was required. A possible explanation is that the presence of oedema decreases the current density available for stimulation of the nerve. The application of pressure significantly reduced the supramaximal current for patients with oedema by approximating the stimulus to the nerve and increasing the available charge. Without the application of pressure, there were a number of patients for whom the supramaximal current was greater than the maximum output of the electromyograph (100 mA). After the application of firm pressure over the stimulating electrodes, the SMC was within the 100 mA range.

Beemer and Reeves evaluated eight neuromuscular monitors and demonstrated that only three (Fisher Paykel A400, Myotest DBS, and Rutter 4B) were able to deliver a constant current over a wide range of skin impedance and that of those the highest deliverable current was 86 mA.[6] We have demonstrated that in critically ill patients a supramaximal stimulus may require a higher current and that peripheral oedema may impair accuracy of neuromuscular monitors in this environment. The mechanism for the increase in supramaximal current is likely to be a dissipation of current in oedematous tissues. The actual current presented at the nerve is unknown and we advise caution in the application of large currents for neuromuscular monitoring.

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Contamination of coagulation tests with heparin from blood gas samples

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We investigated the possibility that samples of blood could be contaminated by heparinized blood gas syringes, giving spurious results in coagulation tests. We collected coagulation test samples before (n=5) and after (n=13) blood gas sampling from a venous cannula in a volunteer. The results of activated partial thromboplastin time (APTT) tests were compared between control samples and samples taken before and after blood gas sampling. The median APTT after blood gas sampling was 71 s, significantly higher than before (median 34 s, P<0.05). We conclude that heparin from blood gas sampling syringes can contaminate coagulation tests. Heparinized samples for blood gas analysis should be obtained after coagulation test samples have been obtained.

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Blood samples are often taken from indwelling catheters during anaesthesia and in intensive care. Contamination of coagulation tests with heparin left in such catheters is well known.[1 2] Heparin-free flush solution is now used routinely to stop this source of contamination. When we obtained some apparently spurious coagulation test results, we thought that heparin from blood gas syringes could contaminate the samples taken for activated partial thromboplastin time (APTT) measurement and investigated this possibility in a volunteer.

Methods and results

After the hospital ethics committee had given permission for the study, a 16-gauge i.v. cannula (Insyte; Becton Dickinson) was inserted into the median cubital vein of one of the investigators (J.M.B.). A three-way tap (Connecta Plus 3; Becton Dickinson) was connected to the cannula via a 60 cm arterial pressure tube (Arterial Pressure Tubing; Abbott Ireland). A series of samples was obtained from the three-way tap. Group A (n=5) was the control group, in which coagulation samples were obtained using a fresh sampling connector (Venoject Luer adapter) after 2.5 ml of blood had been discarded. Blood gas samples were obtained using 3 ml Preset syringes (Becton Dickinson, Product No. 365313) filled to the self-venting mark (0.6 ml). Group B (n=13) was the test group, in which the coagulation samples were obtained immediately after blood gas sampling (without flushing or discarding). Coagulation test tubes (3.5 ml 9 NC; Greiner Labortechnik) containing 3.2% sodium citrate were used for coagulation tests. The blood samples were obtained with the Vacutainer system (Venoject Luer adapter, Terumo). The coagulation analysis was performed with ACL Futura Plus Instrumentation Laboratory analysers (Beckman Coulter Australia, Australia). The normal range for the APTT for our laboratory is 25–38 s.

The Mann–Whitney U test was used to compare the results using the PEPI statistical package (Abramson and Gahlinger). An arbitrary value of 300 s was allocated if the values were greater than 300 s.

Table 1 shows the results of the coagulation tests. APTT values after blood gas sampling (group B) were significantly longer (median 71.3 s) than control values (group A) (median 33.9 s; P<0.05).

Comment

We found that heparin from blood gas syringes can contaminate coagulation test samples. The arbitrary use of

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Table 1 APTT results for control (A) and test (B) groups

	Group A (*n*=5)	Group B (*n*=13)
Median APTT (s)	33 9	71 3
Range (s)	32.9 to 35 4	32.7 to >300
Interquartile range (s)	33 9 to 34 6	55.3 to 106 4

300 s for APTT values >300 would tend to reduce any difference between groups. In clinical practice, the degree of contamination will depend on several factors. The amount of heparin in blood gas syringes varies (>80 units with Becton Dickinson 3 ml Preset syringes), and this and the volume of blood drawn into the syringe will determine the heparin concentration in the syringe. The amount of blood remaining in the hub of the three-way tap after blood gas sampling will vary with blood viscosity and depend on how the syringe is removed. We found contamination, but a larger study would be needed to estimate the magnitude of the error. Samples for coagulation tests should be taken before samples are taken with syringes containing anticoagulant.

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Randomized prospective double-blind placebo-controlled trial of effect of intravenous ondansetron on intraocular pressure during ophthalmic surgery

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The effect of i.v. ondansetron, before induction of anaesthesia, on intraocular pressure (IOP) in patients undergoing cataract surgery was investigated. Forty patients (two groups of 20) received either ondansetron 4 mg (treatment group) or 0.9% saline (placebo group) in a double-blind controlled manner. There were no significant differences in IOP between the groups. Ondansetron had no significant effect on IOP during the study period.

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Keywords: eye, intra-ocular pressure; vomiting, antiemetics, ondansetron

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Over the last decade the use of local anaesthetic techniques for intraocular operations has increased. However, there remains a need for general anaesthesia in a number of patients undergoing intraocular surgery. Control of intraocular pressure (IOP) is necessary in these cases. Nausea and vomiting following anaesthesia are recognized postoperative complications in eye surgery. Both can increase IOP. Any increase in IOP especially in perforating eye injuries or glaucoma, may be deleterious to patient's vision. Therefore, many anaesthetists routinely give antiemetic agents before or during anaesthesia for ophthalmic surgery.

Ondansetron is a commonly used antiemetic drug with few side-effects.[1] It has a proven efficacy to prevent and treat postoperative nausea and vomiting in non-ophthalmic

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Table 1 Mean (SD) values of IOP, HR=heart rate and arterial pressure (SAP=systolic, DAP=diastolic) Significant change from: *, baseline, †, pre-intubation within group, or ‡, difference between groups ($P<0.05$). 1=Before administration of test solution; 2=after administration; 3=after induction/before intubation; 4=immediately after intubation; 5=5 min after intubation

Variable	1	2	3	4	5
IOP (mm Hg)					
Saline	20 (4.5)	18 (5.4)	14 (5.9)*	20 (5.7)†	14 (4.9)*
Ondansetron	18 (5.3)	17 (5.4)	14 (7.1)	18 (7.0)	14 (5.7)
HR (beat min^{-1})					
Saline	80 (16.7)	79 (17.2)	78 (20.5)	91 (21.2)	80 (16.6)
Ondansetron	70 (11.5)‡	69 (12.7)‡	87 (13.4)	80 (20.1)	76 (14.1)
SAP (mm Hg)					
Saline	149 (27)	143 (24.2)	131 (31.0)	158 (22.5)	128 (25.7)
Ondansetron	148 (28)	145 (25.3)	140 (29.7)	165 (21.9)	135 (24.5)
DAP (mm Hg)					
Saline	87 (9.9)	82 (12.1)	78 (17.5)	95 (16.2)	77 (14.9)
Ondansetron	79 (13.0)‡	80 (12.7)	84 (18.5)	96 (14.0)	72 (13.2)

and ophthalmic surgery.[2 3] However, its effects on IOP are unknown. Consequently, this study was undertaken to ascertain the effects of i.v. ondansetron on IOP.

Methods and results

This was a randomized, placebo-controlled, double-blind study. Approval from the Research Ethics Committee was given. Forty patients, ASA class I–III, undergoing elective cataract surgery under general anaesthesia, were recruited after a written informed consent was obtained. They were premedicated with temazepam 0.15 mg kg^{-1} 90 min before surgery. Patients were randomly allocated to one of two groups of 20. Twenty patients per group represents a sample size sufficient to detect a difference in IOP of 4.2 mm Hg with 90% power, based upon a SD of 4 mm Hg.[4]

Patients under 18 yr of age, ASA class IV or V, who vomited or received antiemetics before surgery were excluded. Those with a history of substance abuse, glaucoma, those who were pregnant or breast-feeding or had a contraindication to the use of ondansetron were also excluded.

IOP was measured using a calibrated Keeler pulsair 2000 non-contact applanation tonometer (Keeler Plc, UK). It is a simple instrument to use with an accuracy of ±1 mm Hg.[5] IOP measurements were obtained from the eye not undergoing surgery. Baseline IOP, arterial pressure (AP) and heart rate (HR) were measured. Ondansetron 4 mg or 0.9% saline as 2 ml solution was administered intravenously. Five minutes later, IOP, AP, and HR were measured. Anaesthesia and muscle relaxation were achieved with thiopentone 2–5 mg kg^{-1} and atracurium 0.5 mg kg^{-1}. Patients' lungs were ventilated to normocapnia with 35% oxygen in nitrous oxide and 1% isoflurane. Further IOP, AP, and HR were measured immediately before, immediately following and 5 min after intubation.

After the study period, droperidol 0.02 mg kg^{-1} was given and a rescue antiemetic was prescribed postoperatively. After surgery, muscle relaxation was reversed with glycopyrrolate and neostigmine.

Homogeneity of variance was established using Levene's test and the data were compared using Student's *t* and chi-squared tests according to variables. Within group analysis was performed with ANOVA with Bonferroni's correction. P-value <0.05 was considered significant.

There were no significant differences between the ondansetron and the saline groups in terms of age, gender, mean baseline IOP, and systolic AP (SAP) (Table 1). Baseline HR and diastolic AP (DAP) were significantly lower in the ondansetron group than the saline group ($P<0.05$).

No significant differences in mean IOP values were noted between the ondansetron and the saline groups throughout the study period (Table 1). In the ondansetron group, mean IOP decreased below baseline value following induction ($P>0.05$). Although IOP increased immediately following intubation. the increase was not significant and was absent at 5 min after intubation. Similar observations were seen in the saline group, but the changes in mean IOP were significant ($P<0.05$). With the exception of the baseline differences and mean HR at 5 min post-administration of ondansetron, cardiovascular variables were similar in the two groups.

Comments

Although baseline mean HR and DAP were significantly different between groups, the difference was small and clinically unimportant. Furthermore, there was no significant difference in either baseline mean IOP or SAP in the two groups. A possible explanation could be that five patients in the ondansetron group were receiving calcium-channel blockers *vs* none in the saline group. This does not appear to have influenced the results as the usual cardiovascular changes that follow tracheal intubation were observed in both groups (Table 1).

The purpose of this study was to ascertain the effects of ondansetron on IOP, not to assess its efficacy as an antiemetic, which has been reported previously.[1 2] Ondansetron was associated with cardiovascular stability[6] and no effect on intra-cranial or cerebral perfusion pressures[7] and, therefore, unlikely to affect IOP. This study confirms that ondansetron does not increase IOP before, or during, induction of anaesthesia for ophthalmic surgery. These findings contrast with other antiemetics used in ophthalmic anaesthesia, which are associated with side effects. Metoclopramide may increase IOP[8] and droperidol causes hypotension, postoperative drowsiness and confusion in elderly patients.[9] The former agent should not be given before induction of anaesthesia in patients with perforating eye injuries, as it may lead to loss of intraocular contents. The latter should be used cautiously in aged patients.

In conclusion, IOP appears to be stable following i.v. administration of ondansetron before induction of anaesthesia. We suggest that ondansetron can be safely given before induction for the prevention or the treatment of nausea and vomiting in patients in whom it is essential to minimize changes in IOP such as those with perforating eye injuries or glaucoma.

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Evaluation of the Greenbaum sub-Tenon's block

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A prospective, randomized blind study was conducted in 40 patients undergoing phacoemulsification and posterior chamber intraocular lens implantation. They received anaesthetic infiltration of 2% lidocaine with 1:200 000 epinephrine and hyaluronidase 150 U ml^{-1} in a volume of 2, 3, 4 or 5 ml into the sub-Tenon's fascial space through a Greenbaum cannula after a conjunctival incision. Reduction of ocular movements, anaesthesia, pain on injection and any incidental complications were recorded. Akinesia and anaesthesia occurred within 5 min with 4 and 5 ml of local anaesthetic, and no supplementary injections were required. There were marked reductions in the frequency of forced eyelid movements with these volumes. Chemosis and conjunctival haemorrhage were noted in the majority of patients but caused no intraoperative problems. Approximately 10–15% of patients reported slight discomfort at the time of injection. Four to 5 ml of 2% lidocaine with 1:200 000 epinephrine and 150 U ml^{-1} of hyaluronidase is the optimum volume to achieve adequate akinesia, anaesthesia and reduction of lid movements during the Greenbaum sub-Tenon's block.

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Regional anaesthesia is widely used for ophthalmic surgical procedures and blocks are most commonly evaluated in patients undergoing cataract surgery. There is substantial international variation in the provision of ophthalmic regional anaesthesia for cataract surgery, both akinetic and non-akinetic techniques being used.[1–3] At present, there is no technique that can be described as ideal. There is no standard method of formal assessment of anaesthesia and any inadequacy is often only apparent during surgery. The assessment of the extent of anaesthesia is particularly difficult when topical agents are used to produce surface anaesthesia, leading most investigators to rely on the development of akinesia as a marker of sensory, as well as motor, blockade.

This study was designed to evaluate and assess the Greenbaum technique and the optimum volume of local anaesthetic required to achieve maximum akinesia.

Methods and results

After having obtained Local Hospital Research Ethics Committee approval, we recruited 40 consecutive patients undergoing phacoemulsification cataract surgery into a prospective randomized blind study. Exclusion criteria were previous intraocular surgery, apparent ocular pathology other than age-related cataract and inability to communicate during surgery. After they had given informed consent, the patients were randomized to receive 2, 3, 4 or 5 ml of 2% lidocaine with epinephrine 1:200 000 and hyaluronidase 150 U ml^{-1} into the sub-Tenon's fascial space using Greenbaum's cannula.

An independent observer, who was unaware of the volume used, assessed the quality of block. The patients were assessed for residual ocular movements in the superior, inferior, medial and lateral directions (movement scores: maximum, 3; moderate, 2; minor, 1; no movement, 0; range of 0–12 for each assessment) and forced lid opening and closure before the block and 2, 5 and 10 min after injections. If the akinesia score was >4 or judged inadequate for surgery at 10 min, a repeat injection consisting of a further 2 ml was given. Pain during the injection of local anaesthetic was assessed using a verbal rating score (no pain, 0; worst imaginable pain, 10). The surgeons were asked to note any discomfort or other complication that occurred during surgery. No sedation was used. Data were analysed using analysis of variance for repeated measures, Student's *t*-test, the χ^2 test and the Mann–Whitney *U*-test as appropriate. Values of $P<0.05$ were considered statistically significant.

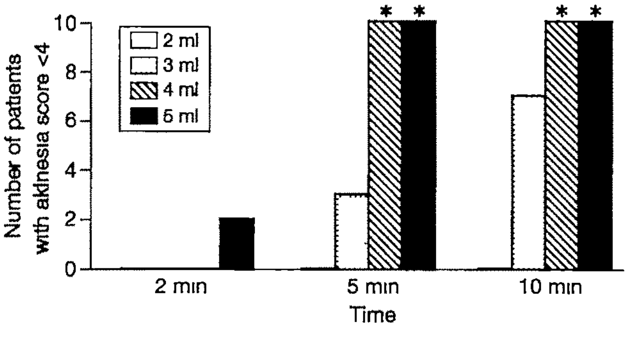

Fig 1 Effect of volume of local anaesthetic injected on time to onset of akinesia ($P<0.05$).

Patient data were comparable in all groups with respect to age, weight and axial length. The onset of akinesia was directly related to the volume of local anaesthetic injected (Fig. 1). None of the patients who received 2 ml had an akinesia score of <4 at 10 min. Twenty and 60 per cent of patients receiving 3 ml had an akinesia score of <4 at 5 and 10 min respectively. All patients receiving 4 or 5 ml had an akinesia score of <4 at 5 min, and this was statistically significant ($P<0.05$).

Lid opening and closing were both present in all patients receiving 2 ml of local anaesthetic but were markedly reduced or abolished in the other groups within 10 min and the onset was faster as the volume increased. All patients receiving 2 ml of local anaesthetic required a repeat injection but the requirement for repeat injections fell as the volume of local anaesthetic increased. None of the patients who received 4 or 5 ml of local anaesthetic required supplementary injection. None of the patients who had complete akinesia felt any pain or discomfort during surgery. Chemosis increased in incidence as the amount of local anaesthetic injected increased but did not cause any problem with surgery. A minor degree of conjunctival haemorrhage was observed in all cases, but the operating surgeons did not find this to be a problem. Fifteen per cent of the patients reported a minor degree of discomfort during the injection but their score was never >3 on the verbal rating score.

Comment

The original Greenbaum technique[4] used diathermy and did not lead to akinesia. Small volumes of local anaesthetic were used without hyaluronidase. The technique appears to be simple, safe and effective but anaesthetists may be reluctant to use diathermy and the non-akinetic nature of the block leads to concern about the assessment of anaesthesia before the start of surgery. The assessment of anaesthesia is particularly difficult when topical agents are used to produce surface anaesthesia, so most investigators rely on the development of akinesia. The usual commercially available cannulae for sub-Tenon's injection are made of metal and they are longer than the Greenbaum cannula, which is short, flexible, plastic and non-traumatic.

Inferonasal quadrant access is the method described most commonly in the literature because the dissection is away from the cataract incision area.[5] [6] In our experience of the use of this technique in 40 patients, it was easy to learn and perform. Injection of 4 or 5 ml of local anaesthetic produced effective anaesthesia and nearly complete akinesia within 5 min in all patients. We encountered no serious problems and the post-operative period was uncomplicated.

However, this technique has limitations. The injection site was slightly larger than the cannula size, although perhaps the use of diathermy would have limited the widening of the incision area, which increased as a result of traction during the injection. This also led to loss of local anaesthetic solution during the injection. Minor conjunctival haemorrhage was present in all patients, which is more frequent than the 56% reported in other papers.[5] [6] Chemosis was another common feature of this technique. The incidence and extent of chemosis increased as the volume of the local anaesthetic increased. The length of the cannula may have contributed to this phenomenon. We agree with Greenbaum that the use of diathermy may be worthwhile in attempting to reduce the incidence of conjunctival haemorrhage and chemosis. However, it is expensive and we believe that most anaesthetists would not use it.

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Comparison of patient-controlled epidural analgesia with and without night-time infusion following gastrectomy

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To assess the analgesic efficacy and side effects of a supplemental night-time infusion in patient-controlled epidural analgesia (PCEA) after gastrectomy, we carried out a randomized, double-blind study. The number of requests were lower ($P<0.005$) in the PCEA plus night-time infusion group than in the PCEA alone group during the postoperative nights. Patients who had a PCEA plus night-time continuous infusion, slept with fewer interruptions than those who had only the PCEA. VAS pain scores on coughing were significantly lower ($P<0.05$) in the PCEA plus infusion group than in the PCEA alone group during the night following postoperative day 1. In conclusion, a night-time infusion in PCEA following gastrectomy decreases the incidence of postoperative pain, provides a better sleep pattern, and reduces the degree of the pain associated with coughing during the night.

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In a study of patients' experiences of pain and sleep, pain was the most common cause of night-time sleep disturbance and the use of analgesics was the effective method of restoring sleep in most patients. Analgesics were given most often during two time intervals: between 08:00 and 12:00, and between 20:00 and 00:00.[1] Patients who use a demand-only patient-controlled epidural analgesia (PCEA) may have to demand analgesia frequently during the post-operative nights and a night-time infusion from 20:00 to 08:00 may improve the incidence of night-time pain and sleep disturbance. However, to our knowledge, no reports have compared the analgesic efficacy of PCEA alone with that of PCEA with a supplemental night-time infusion following gastrectomy. We carried out this randomized, double-blind study to evaluate the efficacy of night-time infusion in PCEA with a mixture of fentanyl and bupivacaine after gastrectomy.

Methods and results

After obtaining institutional ethics committee approval and written informed consent, we undertook this prospective, randomized, double-blind study in 40 patients undergoing distal or total gastrectomy. We explained the operational aspects of the PCA pump to each patient preoperatively. Exclusion criteria included ASA >3, preoperative opioid administration, clinical or laboratory contraindications to epidural catheter insertion, inability to use the PCA device, and/or allergy to any of the medications.

An epidural catheter was inserted through the T9–10 interspinous space into the epidural space. Anaesthetic induction and intubation was performed with i.v. fentanyl, thiopental, and vecuronium bromide. Anaesthesia was maintained with a propofol infusion, sevoflurane, and oxygen in air. Additional intraoperative epidural analgesia was provided with mepivacaine or bupivacaine. No opioids were used during intraoperative anaesthesia.

A PCA pump containing fentanyl 5 μg ml^{-1} and 0.1% bupivacaine was connected to the epidural catheter and started as soon as the patient was extubated. The PCEA alone group received 5-ml bolus on demand, with a lockout interval of 15 min. In addition to the intermittent bolus doses, the PCEA plus infusion group received 2 ml h^{-1} of the bupivacaine/fentanyl mixture during the nights (from 20:00 to 08:00 on the day of surgery and on the first postoperative day (POD1)). During the night or if the patient's oxyhaemoglobin saturation by pulse oxymetry (Sp_{O_2}) was less than 94%, the patient received oxygen via nasal cannula. When the patients complained of unsatisfactory pain relief, 1% mepivacaine 3–5 ml was injected via the epidural catheter until they were pain free. The anaesthestist and nurse investigators were blinded with respect to the mode of administration.

The number of patient requests for analgesia (demand) was recorded from the pump hourly during the time from the start of the study to 14:00 on the second postoperative day (POD2). We calculated the average hourly consumption that includes the infusion and patient demands during the time from the start of the study to 20:00 on the day of surgery, during the night, and in each 6-h interval during the daytime. VAS pain scores both at rest and on coughing were recorded on a 100-mm linear scale, nausea and pruritus were assessed using a 4-point rating scale (0: none; 1: slight; 2: moderate; 3: severe) and objective motor block was assessed using the Bromage score, at 20:00 on the day of surgery, at 8:00, 14:00, and 20:00 on POD1, and at 8:00 and 14:00 on POD2. Sedation was assessed using a 4-point scale (0: eye open spontaneously; 1: eye open to speech; 2: eye

Table 1 Hourly number of demands, hourly drug consumption, VAS at rest and on cough data are expressed as mean (SD). PCEA: patient-controlled epidural analgesia.*$P<0.005$, **$P<0.05$ compared with PCEA alone group. #Solution of 5 μg fentanyl and 1 mg bupivacaine in 1 ml

	Hourly number of demands		Hourly consumption volume (mL)#		VAS at rest (mm)		VAS on cough (mm)	
	PCEA alone	PCEA plus infusion	PCEA alone	PCEA plus infusion	PCEA alone	PCEA plus infusion	PCEA alone	PCEA plus infusion
20 00	0.7(0.4)	0.8(0.5)	3.5(1.6)	3.7(1.3)	25.2(14.1)	25.0(12.8)	41.6(18.9)	41.6(14.9)
8.00 on POD1	0.8(0.4)	0.4(0.3)*	4.1(2.3)	4.2(1.6)	24.3(13.9)	16.8(8.8)	39.2(19.1)	34.8(13.3)
14:00	0.9(0.4)	0.6(0.2)	4.5(2.0)	3.5(1.4)	19.9(7.9)	18.0(9.9)	39.1(15.8)	34.5(10.8)
20.00	0.8(0.4)	0.7(0.3)	3.9(2.0)	3.8(1.7)	20.1(10.1)	19.9(8.2)	37.6(15.6)	37.1(12.8)
08:00 on POD2	0.7(0.4)	0.3(0.3)*	3.6(1.7)	3.8(1.5)	19.9(10.8)	15.2(8.0)	42.5(15.2)	33.9(14.8)**
08.00–14.00	0.6(0.4)	0.5(0.4)	3.0(1.7)	3.1(2.1)	19.9(8.8)	19.5(11.8)	35.3(13.9)	34.8(12.7)

open to shaken; 3: unrousable) at 20:00 on the day of surgery, at 8:00, 14:00, 20:00 on POD1, at 8:00, 14:00 on POD2 and every 1–2 h during the nights. Verbal rating score for sleep pattern was assessed using a 3-point rating scale (0: slept well without PCEA button press; 1: slept well with PCEA button press; 2: could not sleep despite PCEA button press) at 8:00 on POD1 and POD2. Systolic arterial pressure and ventilatory frequency were measured every 1–2 h, and more frequently if the systolic arterial pressure was less than 100 mm Hg or the ventilatory frequency rate was less than 10 breaths min^{-1}.

Continuous data are reported as mean (SD) and analysed using the unpaired two-tailed *t*-test and two-way analysis of variance (ANOVA) for repeated measurements. Ordinal data were reported as incidences and analysed using the Mann–Whitney *U*-test. Patient characteristics were analysed using the unpaired two-tailed *t*-test for parametric variables and the chi-squared test for non-parametric variables. Values of $P<0.05$ were considered statistically significant.

Two patients in each group required additional pain relief and received supplemental epidural boluses of 1% mepivacaine 3–5 ml. However, hypotension did not occur in any patient after supplemental bolus injection. Patient characteristics and operative procedures were comparable between the two groups.

The mean time from the start of the study to 20:00 on the day of surgery was similar between the two groups. The average hourly demand was lower ($P<0.005$) in the PCEA plus infusion group than in the PCEA alone group during the night (Table 1). The average hourly consumption drugs did not differ between the two groups during the study period (Table 1). VAS pain scores on coughing were significantly lower ($P<0.05$) in the PCEA plus infusion group than in the PCEA alone group at 8:00 on POD2. The sleep scores on POD1 in the PCEA plus infusion group were significantly lower than those in the PCEA alone group ($P=0.018$).

The incidence of side effects did not differ between the two groups. No motor block and sensory disturbance were detectable in any patient during the 48-h postoperative period. A ventilatory frequency of less than 10 breaths min^{-1}, sedation score $\geqslant 2$ and haemoglobin oxygen desaturation were not recorded for any patient after commencement of PCEA. Hypotension occurred in two of 20 patients (10%) in each group during the study period.

Comment

The results of the present study indicate that the patients with a night-time infusion had fewer episodes of pain, sleep disturbed, and less pain on coughing than did patients in the PCEA alone group during the night.

We thought a night-time infusion to be more desirable than an all-day infusion, which had produced more itching than PCEA alone group in an earlier study.[2] The incidence of pruritus did not differ between the two groups in our study.

The use of a night-time infusion in a PCEA regimen caused no increase in the incidence of excessive sedation and respiratory depression in our small study; however, respiratory depression was possible during the periods in which the patients were not disturbed by measurements. This emphasizes the need for careful and repeated assessment by experienced staff.

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Postoperative analgesia by epidural methylprednisolone after posterolateral thoracotomy

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The aim of this study was to evaluate the potential analgesic effect of epidural methylprednisolone (MP) after posterolateral thoracotomy (PLT). Adult male patients undergoing PLT for lung

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surgery were included in a prospective, randomized, double blind study. Peroperative analgesia (bupivacaine plus sufentanil) was given by a thoracic epidural catheter associated with general anaesthesia. After surgery, patients received either MP 1 mg kg^{-1} followed by a continuous epidural infusion of MP 1.5 mg kg^{-1} during 48 h (MP group) or 0.9% saline as a bolus injection and continuous epidural infusion (P group). Additional morphine analgesia was administered by i.v. patient-controlled analgesia. Pain was assessed at rest and with mobilization every 4 h after operation during 48 h with a visual analogue scale (VAS). The primary end-point was the total morphine requirements during the 48 first postoperative hour. Twenty-four patients were allocated to MP (*n*=12) and P (*n*=12) groups. Characteristics of the two groups were similar. There were no differences between groups for morphine requirements (median and interquartile range) during the 48 h: 59 mg (40–78) in MP group *vs* 65 mg (59–93) in P group. There were no differences between groups for morphine requirements every 4 h during the 48 h and VAS for pain at rest and evoked pain. No side effects were reported. It was concluded in this small study that these results did not support the use of epidural steroids for postoperative analgesia after PLT.

Br J Anaesth 2001; **87**: 635–8

Keywords: analgesia, postoperative; analgesic techniques, epidural; analgesics anti-inflammatory, steroid; surgery, thoracic

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Posterolateral thoracotomy (PLT), is one of the most painful surgical procedures.[1] Various techniques have been developed and evaluated to treat it, particularly epidural analgesia.[1] Epidurally administered glucocorticoids have been used in rheumatology since the 1960s for treatment of the chronic radicular pain of sciatica as a result of herniated nucleus pulposus.[2] Their more recent use in the treatment of acute pain after laminoarthrectomy has suggested a satisfactory analgesic effect during the postoperative period.[3 4] In this situation, glucocorticoids act probably at the surgical site by a local anti-inflammatory effect. But glucocorticoids may have a central effect.[5] We conducted a prospective randomized, double blind, placebo-controlled clinical study to determine whether methylprednisolone (MP) improved analgesia when administered epidurally in this after PLT.

Methods and results

After approval by the Ethics Committee and written informed consent, 27 adult male patients undergoing lobectomy or pneumonectomy for cancer, were included. The same team surgeon operated all patients by PLT including preservation of the serratus anterior muscle.

The primary end-point was the total i.v. morphine requirements by patient-controlled analgesia (PCA) pump during the first postoperative 48 h. Secondary end-points were the 4-hourly interval morphine requirements during 48 h, visual analogue scale (VAS) pain assessment at rest and mobilization, quality of pain relief appreciated by the patient himself and the incidence of adverse events.

During the preoperative visit, the patient was instructed in the use of the VAS and PCA use. After premedication with hydroxyzine 1.5 mg kg^{-1}, an epidural catheter was inserted at T4–T5 or T5–T6. A mixture of 100 mg bupivacaine with 0.1 mg epinephrine, 20 µg sufentanil and saline solution (total volume of 30 ml), was injected at a rate of 5 ml every 5 min until a block was obtained extending from T1 to T10. General anaesthesia was induced with thiopental 6 mg kg^{-1} and pancuronium bromide 0.1 mg kg^{-1}, orotracheal intubation was performed after local anaesthesia of the glottis, using a double lumen 39–41 tube. Anaesthesia was maintained by inhalation of nitrous oxide and isoflurane. Patients were assigned randomly to two groups the day before surgery. At the end of the operation, patients in the MP group received epidural administration of 1 mg kg^{-1} of MP diluted in 10 ml of saline solution followed by a continuous epidural infusion of 1.5 mg kg^{-1} of MP diluted in 24 ml of saline solution. Patients in the placebo (P) group received identical volumes of saline solution epidurally, followed by a continuous epidural injection at the same rate. The various solutions were administered in double blind manner and maintained for 48 h postoperatively.

An initial morphine-loading dose was given when the patient complained of pain (VAS >3 cm). Titration of 1 mg boluses followed until pain was relieved (VAS <3). Subsequently, the PCA pump was set on PCA mode alone (10-min lockout, 1 mg bolus and no maximal dose).

Haemodynamic data, ventilatory frequency, Sp_{O_2} and level consciousness were evaluated every hour for 48 h. Consciousness was scored on a scale of 1–5 (1= asleep and not wakeable; 2=asleep but wakeable with altered vigilance; 3=asleep but wakeable and vigilant; 4=spontaneously awake; and 5=restless). The patient evaluated his pain (at

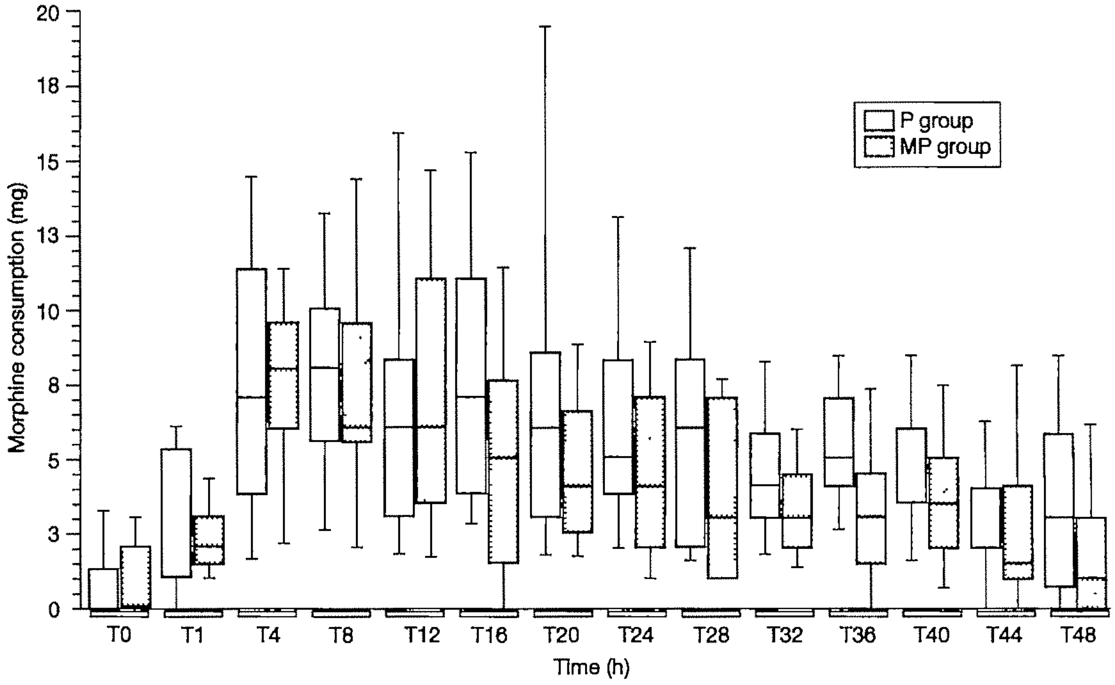

Fig 1 Box-plots of 4 hourly morphine requirements during the first postoperative 48 h. No significant differences between groups (P=0.197).

rest and on coughing) every 4 h using a VAS (0=absence of pain; 10=unbearable pain). The patient evaluated the quality of relief of pain using a questionnaire insufficient, good, excellent at 72 h postoperatively. Adverse effects were recorded during the entire period.

Data are presented as mean (SD) or median with interquartile range. Statistical analysis was performed using the Mann–Whitney rank sum test for comparison of quantitative variables. Multivariate analysis of variance (MANOVA) for repeated measurements was used to compare VAS pain scores and morphine use over time between the groups or within each group throughout the study (Systat IM 7.0 software). The significance threshold for the tests was set at P<0.05.

Three patients were excluded because of misunderstandings with respect to the use PCA or technical failure. Therefore, 24 patients were included in the statistical analysis, 12 in each group. There were no significant differences between the two groups with respect to patient, surgical and anaesthetic characteristics.

Total morphine requirements during the study were not significantly different between the two groups (median 59 (40–78) for MP group and median 65 (59–93) for P group) (Fig. 1).

VAS pain scores at rest and for evoked pain did not differ between groups (P=0.59 and 0.14 for pain at rest or evoked pain, respectively). VAS pain scores at rest were different across time in each group (P=0.029) but no interaction between groups and time was observed. VAS pain scores after evoked pain did not differ significantly within each group throughout the study (P=0.25). Patient satisfaction was not different between groups. There was one case of pruritus and sedation in the MP group, none in P group and two and three cases of nausea and vomiting, respectively, in MP and P groups. No patient experienced bradypnea or required naloxone.

Comment

This prospective, randomized, double blind study showed no significant difference in morphine requirement and pain intensity after epidural administration of MP for the treatment of postoperative PLT pain compared with placebo.

The conclusions of studies concerning the analgesic efficacy of glucocorticoids are controversial. Some data support a central effect of glucocorticoids.[5] Other studies have shown a lack of efficacy.[6] Epidural glucocorticoids have been tested for postoperative pain after spinal surgery. Dexamethasone reduced postoperative lumbar pain after laminoarthrectomy.[3] Epidural administration of methylprednisolone alone or in association with morphine decreased postoperative pain significantly after surgery on spinal stenosis, but not after disk surgery.[4] However, it should be noted that methylprednisolone in spinal surgery acts at the surgical site essentially by a local anti-inflammatory effect. In postoperative pain as a result of PLT, this effect is probably less important.

It is concluded that our data do not support the use of epidural steroids for postoperative analgesia after PLT.

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Serum paracetamol concentrations in adult volunteers following rectal administration

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Paracetamol is usually given in adults at a dose of 10–20 mg kg^{-1} orally or rectally. Work in children suggests that doses of 40 mg kg^{-1} are needed to provide therapeutic concentrations when this drug is used by the rectal route. We have investigated the dose of rectal paracetamol needed to achieve serum concentrations within the accepted therapeutic range of 10–20 μg ml^{-1} in adults. Ten healthy adult volunteers received increasing doses of rectal paracetamol (15, 25, 35, and 45 mg kg^{-1}). Following suppository administration, serum paracetamol concentrations were measured half hourly to 4 h then hourly to 8 h. Sustained concentrations within our therapeutic range were achieved with 35 and 45 mg kg^{-1}. Maximum measured concentrations were 12.5 (10–16), 16.5 (14–20), and 20 (17.5–23) μg ml^{-1}, median (inter-quartile range) after 25, 35, and 45 mg kg^{-1}, respectively. We conclude that doses of 35–45 mg kg^{-1} of rectal paracetamol are needed to achieve sustained therapeutic plasma concentrations in healthy adult volunteers.

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Keywords: analgesics non-opioid, paracetamol; anaesthetic techniques, rectal; adults

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Paracetamol is a safe, cheap and effective analgesic that is widely used. The World Health Organization has recommended that it be used as the starting point for all analgesic regimes. It can be administered orally or rectally and in anaesthetic practice is often used rectally in order to provide postoperative analgesia.

The analgesic therapeutic concentration for paracetamol is not well defined. Plasma concentrations of 10–20 μg ml^{-1} are associated with antipyretic activity.[1] No formal work has been completed to define paracetamol concentrations needed for analgesia. However, previous work has assumed that analgesic and antipyretic concentrations will be similar.[2–5]

Oral paracetamol doses of 10–20 mg kg^{-1} are used in adults and children and provide plasma concentrations within the accepted therapeutic range. However, when given rectally, these doses may be insufficient. Work in children has shown that doses of up to 40 mg kg^{-1} are needed to achieve these target plasma concentrations.[2–4] Similar doses may be needed in adults.

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The aim of our study was to ascertain what dose of rectal paracetamol is needed, in adult volunteers, to achieve plasma paracetamol concentrations of 10–20 µg ml^{-1}.

Methods and results

Following ethics committee approval, 10 ASA I or II adult volunteers were recruited from our anaesthetic departmental colleagues. Exclusion criteria included body mass index greater than 35, pregnancy, regular usage of paracetamol containing medication, intolerance or allergy to paracetamol and abnormal renal or hepatic function. Urea and electrolytes and liver function tests were checked prior to enrolling a volunteer in the study.

Each volunteer took part in the study on four occasions separated by at least 48 h. No paracetamol containing medication was taken for 24 h prior to any of the study days. Volunteers received increasing doses of rectal paracetamol starting with 15 mg kg^{-1}, rising by 10 mg kg^{-1} to a maximum of 45mg kg^{-1}.

Paracetamol is not evenly distributed within standard suppositories. Hence, it was not possible to provide exact paracetamol doses by shaving portions off these suppositories. Each volunteer was weighed and suppositories were specifically manufactured to achieve exact doses. Witepsol was used as the base for these suppositories. Multiple numbers of suppositories were used to avoid any single suppository of greater than 1 g of paracetamol. This is consistent with clinical practice where multiple suppositories are used in order to achieve the most appropriate patient dose. This is important, as it is known that rectal absorption of paracetamol varies with suppository size.

On each day of the study, an i.v. cannula was inserted and a baseline blood sample taken. The suppository was then self administered and serial blood samples taken every 30 min for 4 h and then hourly for a further 4 h. Samples were refrigerated and dispatched to the laboratory as a batch at the end of each day. If any plasma paracetamol concentration had been recorded as greater than 30 µg ml^{-1} that volunteer would not have received further doses.

The assay used to measure plasma paracetamol concentrations was a Cambridge Life Sciences enzymatic assay using a Roches Hitachi multichannel analyser (inter-assay CV 1.1–1.4%, concentration range 0–300 µg ml^{-1}, intra-assay CV 0.5–1%, concentration range 0–130 µg ml^{-1}, dynamic range of the assay 0–378 g ml^{-1}, sample size per assay is 20). The lower limit of detection in our laboratory was 10 µg ml^{-1}.

Concentration *vs* time curves were plotted for all 10 volunteers for each dose of paracetamol received. The median values for each time period at each dose are shown in Figure 1.

Values are not shown for doses of 15 mg kg^{-1} as this failed to achieve median concentrations greater than 10 µg ml^{-1} at any time period and 25 mg kg^{-1} produced concentrations at the lower end of the therapeutic range for a brief period. However, 35 and 45 mg kg^{-1} achieved sustained concentrations within our assumed therapeutic range. These doses resulted in plasma concentrations above 10 µg ml^{-1} for median time periods of 5.5 h (35 mg kg^{-1}) and 6 h (45 mg kg^{-1}). The graphs also show that there is a 1 to 2 h time delay after rectal administration before therapeutic concentrations are recorded. Median (inter-quartile range) maximum measured concentrations (*C*max) and time to maximum concentration (*T*max) are shown in Table 1. The difference between *C*max at all three doses was found to be statistically significant (ANOVA). Based on previous work[2–5] the sample size was determined to provide a difference in *C*max at the 5% significance level.

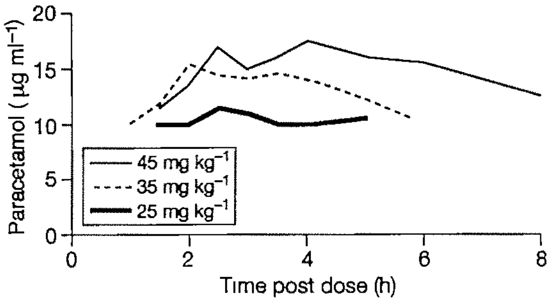

Fig 1 Medial paracetamol concentrations of the 10 volunteers at each time period for each dose given.

Table 1 *C*max and *T*max median (inter-quartile range), *difference between *C*max at 25 mg kg^{-1} and both other doses, ** difference between *C*max 35 mg kg^{-1} and *C*max 45 mg kg^{-1}

Dose (mg kg^{-1})	C_{max} (µg ml^{-1})	T_{max} (h)	*P* value
25	12 5 (10–16)	3.5 (3–5)	<0 01*
35	16 5 (14–20)	3 0 (2 5–5)	
45	20 (17 5–23)	4 25 (2.5–6)	0 03**

Comment

In common with previous work in this area, we have assumed analgesic and antipyretic plasma paracetamol concentrations to be similar.[2–5] Our work has shown that in a population of healthy adult volunteers 15 mg kg^{-1} of rectal paracetamol is probably inadequate. Doses of 35–45 mg kg^{-1}, administered 2 h prior to any desired effect, are needed to achieve sustained concentrations within the accepted therapeutic range of 10–20 µg ml^{-1}. This confirms recent work suggesting 40 mg kg^{-1} of rectal paracetamol is needed to achieve therapeutic serum concentrations.[5] However, this dose was not associated with improved analgesia, leading the authors to conclude that higher plasma concentrations may be needed to provide analgesia than those associated with antipyresis. This contrasts with earlier work showing that rectal doses of 20 mg kg^{-1} of paracetamol do appear to have a clinical useful morphine sparing effect despite probably not providing concentrations within the accepted therapeutic range.[6]

Concern that these higher doses of paracetamol may cause toxicity appears unfounded, the highest serum concentration we measured was 25 μg ml^{-1}, this is well below the accepted toxic concentration of 120 μg ml^{-1}.

The limitation of our assay (lower limit of detection 10 g ml^{-1}) has restricted our ability to perform pharmacokinetic analysis. However, the aim of the study was to ascertain what dose of paracetamol was needed to achieve plasma concentrations of 10–20 g ml^{-1} and our assay was adequate for the purpose of answering this question.

We conclude that doses of 35–45 mg kg^{-1} of paracetamol are needed in adult volunteers to achieve serum concentrations of 10–20 μg ml^{-1}. This is in agreement with data from paediatric studies. However, more work is needed to establish whether this is in fact the target serum plasma for analgesia.

Acknowledgements

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British Journal of Anaesthesia 87 (4): 641–4 (2001)

BJA

CASE REPORTS

Blood pressure manipulation during awake carotid surgery to reverse neurological deficit after carotid cross-clamping

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We describe the management of three patients undergoing awake carotid surgery who developed signs of cerebral ischaemia after carotid cross-clamping. Drug treatment to increase arterial blood pressure above baseline reversed the neurological deficit and an internal carotid artery shunt was not needed. Shunt insertion is less frequent with regional rather than general anaesthesia, and blood pressure control can reduce this even more. Coincidentally, one of the patients, who gave a history of angina of effort after walking 100 m, complained of chest pain after cross-clamp release. This was treated successfully with sublingual nitroglycerin before ST segment changes became apparent on the ECG. These reports suggest that regional anaesthesia for carotid surgery allows potential complications to be identified earlier than under general anaesthesia using reports from the patient, so that treatment may be modified to prevent morbidity and even mortality.

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Keywords: surgery, carotid endarterectomy; anaesthetic techniques, regional, cervical plexus block; arterial blood pressure, control

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The choice of anaesthetic technique for carotid endarterectomy (CEA) is controversial.[1] [2] Proponents of general anaesthesia say the advantages are cerebral protection from general anaesthetic agents, control of the airway and ventilation, and patient comfort. Recently, regional anaesthesia has attracted considerable interest, with suggestions that it reduces per operative morbidity and mortality.[3] [4] Regional anaesthesia facilitates neurological monitoring during cross-clamping of the internal carotid artery (ICA), although there is also evidence of improved haemodynamic stability[5] [6] and, perhaps, less cardiovascular morbidity and mortality.[7]

Regional anaesthesia is associated with less use of ICA shunts[8] than general anaesthesia, in which many surgeons routinely use a shunt on all patients. This may be of value, as shunting has inherent disadvantages.[9] Signs of impending cerebral ischaemia in an awake patient are more sensitive and specific than the indirect indicators used during general anaesthesia, such as transcranial Doppler ultrasound, EEG processing and evoked potential monitoring.[10] [11] Thus, a shunt is only used if neurological deficit develops after ICA cross-clamping. Some surgeons prefer an awake patient because of the reassurance of being able to converse with the patient with the ICA cross-clamped.

The awake technique allows the anaesthetic management to be changed to treat ongoing problems by feedback from the awake patient. The following three case reports illustrate such dynamic management.

Case 1

A 65-yr-old ASA 3 male patient underwent left CEA under cervical plexus block. He had suffered a cerebrovascular accident 8 weeks previously in the form of hemiplegia and expressive dysphasia, from which he had made a full recovery. He had non-insulin-dependent diabetes mellitus and hypertension, controlled with amlodipine 10 mg once daily. He had 70–80% stenosis of the left ICA and <50% stenosis of the right ICA, assessed by carotid Duplex scan. His unpremedicated arterial blood pressure, recorded on the ward and in the anaesthetic room before sedation, was approximately 155/80 (mean 105 mm Hg). Perioperative monitoring consisted of five-lead ECG, invasive arterial blood pressure, oxygen saturation and end-tidal carbon

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dioxide estimation from within the oxygen facemask. No additional cerebral monitoring was used apart from the awake patient's neurological state. The patient was sedated with a target-controlled infusion (TCI) of propofol administered via a Graseby 3500 Pump at up to 1.2 μg ml^{-1} predicted plasma concentration during placement of the regional blocks and intravascular lines and the dissection phase of the operation. This was switched off once dissection was complete.

Our usual practice during awake CEA is for the anaesthetist to administer heparin 50 unit kg^{-1}, then the surgeons cross-clamp the ICA for 2 min while the anaesthetist observes the patient closely for signs of cerebral ischaemia, such as altered level of consciousness, confusion, dysphasia or altered contralateral grip strength. If there is no neurological change, then arteriotomy and endarterectomy proceed directly. If there is evidence of cerebral ischaemia, the clamp is released while a Pruitt–Isihara shunt is prepared and inserted electively.

In this case, within 30 s of trial cross-clamping, the patient developed subtle neurological changes. He was a few seconds slower in responding to questions and did not know which day of the week it was. We have seen previously that this may be the first or only sign of impending cerebral ischaemia. At this time, the TCI pump displayed a plasma propofol concentration of 0.1 μg ml^{-1}; blood pressure was 140/75 (mean 97 mm Hg) and pulse 55 beats min^{-1}. Because his mean blood pressure was marginally (7%) lower than baseline, we decided to increase this to see whether this could reverse the neurological effects. Two doses of ephedrine 3 mg were given, together with 0.9% NaCl 250 ml. Blood pressure rose to 190/90 and heart rate to 70 beats min^{-1}. The patient's neurological condition improved and the delay in response was reduced, and he was able to work out which day of the week it was (Thursday). After the patient had been reassured and after discussion with the surgeons, endarterectomy proceeded uneventfully without the use of a shunt. A Goretex patch angioplasty was performed before the clamps were released with a total cross-clamp time of 52 min. During this time, ephedrine and phenylephrine were given as required to maintain blood pressure at or above 165 systolic. A total of ephedrine 12 mg and phenylephrine 0.5 mg was administered during the cross-clamp period.

After cross-clamp release, the remainder of the operation proceeded uneventfully. The patient was kept in recovery for 2 h for close neurological and haemodynamic assessment, after which he was sent to the ward. He was discharged home on the second post-operative day.

Case 2

A 73-yr-old female underwent left CEA under deep cervical plexus block. She gave a history of angina of effort after 100 m, orthopnoea and hypertension. Medications included isosorbide mononitrate, captopril 12.5 mg and bendrofluazide 10 mg daily. She had sustained a non Q-wave myocardial infarction 10 yr previously. She had 95% stenosis of the left ICA and 30% stenosis of the right ICA, as assessed by carotid Duplex scan. Baseline arterial blood pressure was 175/95 (mean 122 mm Hg) and pulse was 65 beats min^{-1}. TCI propofol was given at up to 1.0 μg ml^{-1} predicted plasma concentration during regional block insertion but was switched off once dissection was complete.

In this case, the 2 min trial cross-clamp was uneventful, but 25 min after arteriotomy the patient became dysphasic and confused. Arterial blood pressure at this time was 155/75 (mean 108 mm Hg) and pulse 72 beats min^{-1}. Metaraminol 0.25 mg was given, which increased the pressure to 195/95. The patient's symptoms resolved completely and endarterectomy proceeded uneventfully without shunt insertion being needed. Because the internal carotid artery was of sufficient calibre, the patch angioplasty was not done and so the cross-clamp time was only 29 min. A total of five boluses of metaraminol 0.25 mg were given to maintain blood pressure until the end of the operation. After release of the cross-clamp, the patient complained of discomfort in her left chest and arm similar to her angina, although there was no change in the ST segment in leads II and V5. This pain resolved rapidly with sublingual nitroglycerin spray and reassurance. The patient was kept in recovery for 2 h for close observation as before. A 12-lead electrocardiogram was unchanged from before surgery. Her recovery was uneventful and she was discharged home on the third post-operative day.

Case 3

A 68-yr-old man with a dilated cardiomyopathy underwent left carotid endarterectomy under cervical plexus block. He had >90% stenosis of the left ICA and 25% stenosis of the right ICA, as assessed by carotid Duplex scan. Unpremedicated baseline arterial pressure in the anaesthetic room was 135/75 (mean 95 mm Hg). The trial cross-clamp period was uneventful, but 5 min after arteriotomy the patient became dysphasic and confused. Arterial blood pressure at this time was 125/65 (mean 85 mm Hg) and pulse 83 beats min^{-1}. Phenylephrine 0.25 mg was administered, which elevated the pressure to 160/95. The patient's speech improved transiently. However, when arterial pressure fell to 140 systolic, dysphasia and confusion developed again and, in addition, right arm weakness. Incremental increases in the systolic blood pressure to 165 mmHg with phenylephrine reversed these deficits and enabled completion of the endarterectomy without need for the ICA shunt. A total of 2.5 mg phenylephrine was administered. The patient was kept in recovery for 2 h for close observation as before and discharged on the second post-operative day.

Discussion

The crucial feature in these three cases was the fact that none of the patients was hypotensive by conventional criteria when they demonstrated features of cerebral ischaemia. However, increasing and keeping blood pressure to normal or above normal improved cerebral circulation, so that shunting was not required during carotid cross-clamping. The mechanism is presumably an increase in the pressure gradient across the circle of Willis and collateral cerebral circulation. Treatment to increase blood pressure, by as much as 25% above baseline for all patients, has been described during CEA under general anaesthesia previously.[12 13] This has some cardiovascular risk and increases the risk of myocardial ischaemia in patients under general anaesthesia,[14 15] as the incidence of ischaemic heart disease is great in this population. Regional anaesthesia certainly does not abolish the risk of myocardial ischaemia,[16] but it may perhaps reduce it.[5 7] It is more logical to augment blood pressure only when required.[15] The dose of vasopressor/inotrope may be titrated against the patient's blood pressure until the neurological deficit is reversed, while at the same time the patient's cardiovascular condition is monitored closely.

The choice of vasopressor depends on pre-existing disease and previous medication. Ephedrine could be used if the patient is already bradycardic, for example with β-blockers; phenylephrine or metaraminol could be used otherwise.

Of the potential benefits of awake carotid artery surgery, reducing the requirement for ICA shunt insertion is the best proven. Under general anaesthesia, shunt rates vary considerably from 0 to 100%,[17] but the mean rate is greater than the 10–15% reported for awake carotid surgery.[18 19] Manipulation of blood pressure can reduce the requirement for shunting still further, which may be beneficial because of the risks of shunt insertion.[9] These include prolongation of the cross-clamp time; cerebral ischaemia during shunt insertion and removal; risk of embolic stroke by dislodgement of plaque material during shunt insertion; and sudden profound blood loss and hypotension as a result of accidental dislodgement of the shunt. Finally, patch angioplasty is technically more difficult for the surgeon when suturing around a shunt.

In our second case, the patient developed angina as well as neurological impairment during the operation and the patient's conscious state alerted us to her myocardial ischaemia. Treatment was given and the problem reversed before changes in the ECG or the patient's haemodynamic status became apparent.

We consider that, with an awake patient, the anaesthetist has more options and more information to make perioperative decisions about a patient's management when they develop cerebral or myocardial ischaemia after carotid cross-clamping. In high-risk patients, such as those undergoing carotid surgery, this could contribute to differences in morbidity and mortality between regional and general anaesthesia.

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Cardiac arrest associated with use of an argon beam coagulator during laparoscopic cholecystectomy

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We describe a cardiac arrest during use of an argon beam coagulation (ABC) system in an 82-yr-old woman having laparoscopic cholecystectomy under general and epidural anaesthesia. Intra-abdominal pressure (IAP) was controlled to less than 12 mm Hg during a carbon dioxide gas pneumoperitoneum and at first the operation was uneventful. When the ABC system (gas flow 6 litre min^{-1}) was used to control local bleeding in the liver bed abdominal pressure increased rapidly to over 20 mm Hg and, 1 min later, the end-tidal carbon dioxide decreased to zero, followed by bradycardia and cardiac arrest. At once, an emergency laparotomy was performed and resuscitation begun. A mill-wheel murmur was heard on auscultation, leading to suspicion of argon gas embolism. Fortunately, recovery was completed with no neurological deficit. Anaesthesiologists should consider showed that argon gas embolism can occur with the ABC system during laparoscopic surgery.

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Argon beam coagulation (ABC), in which electrosurgical coagulation is produced by a jet of inert argon gas encompassing an electrofulguration arc, is a useful technique during laparoscopic surgery. However, when ABC systems are used in closed cavities, such as in laparoscopic procedures, there is a risk of argon gas embolism caused by intra-abdominal over-pressurization.[1–3] We report a cardiac arrest during laparoscopic surgery using an ABC system, when pulmonary argon gas embolism was strongly suspected.

Case report

An 82-yr-old, 160-cm, 48-kg woman with no history of cardiopulmonary disease or deep venous thrombosis was to undergo laparoscopic cholecystectomy. Her pre-operative chest radiograph showed nothing of note and her electrocardiogram revealed only asymptomatic IRBBB. She was not premedicated for the surgery. After insertion of a peripheral i.v. canula, an epidural catheter was placed at the Th10–11 interspace. The epidural catheter position was checked with a test dose of 60 mg mepivacaine with 15 µg epinephrine. Before induction of anaesthesia arterial pressure was 132/78 mm Hg, and heart rate was 68 beats min^{-1}. After pre-oxygenation, 1 mg vecuronium and 50 µg fentanyl were given intravenously followed by 70 mg propofol, and 5 mg vecuronium to facilitate tracheal intubation. A continuous electrocardiogram, pulse oximetry, end-tidal carbon dioxide and non-invasive blood pressure were monitored. Anaesthesia was maintained with sevoflurane and nitrous

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oxide in oxygen, and 50 mg mepivacaine was administered intermittently via the epidural catheter. Additional vecuronium (1 mg) was given every 20 min. A pneumoperitoneum (surgical carbon dioxide insufflator, Type A5645, Olympus Optical Co. Ltd, Tokyo, Japan) was created by insufflation of carbon dioxide gas via a trocar 1 cm above the navel. Intra-abdominal pressure was regulated to less than 12 mm Hg. End-tidal carbon dioxide was kept within the range 30–35 mm Hg. Approximately 1 h after the beginning of the operation, the surgeon began to use an ABC (Conmed 6500; Conmed, NY, USA: gas flow 6 litre min^{-1}) while resecting between liver bed and gall bladder. This was done to control local bleeding because the monopolar electrocautery was ineffective. Soon after this application of ABC, intra-abdominal pressure increased rapidly to more than 20 mm Hg and, 1 min later, the waveform of the capnogram suddenly disappeared. This was followed by bradycardia (HR=20–30 beats min^{-1}) and a decrease in systolic arterial pressure from 120 to 72 mm Hg. At once, 8 mg ephedrine and atropine 0.5 mg were administered intravenously, and ventilation with 100% oxygen was started. At the same time, the pneumoperitoneum was discontinued and the surgeon started an emergency laparotomy to control bleeding. Active bleeding was not found. In spite of these efforts, progressive arterial desaturation developed and cardiac arrest occurred. A mill-wheel murmur was heard on auscultation of the chest. The patient was moved to the head-down position because pulmonary gas embolism was strongly suspected. External cardiac massage, epinephrine (four doses of 1 mg i.v.) and 700 ml of colloid were given. Subsequently, a cardiac rhythm reappeared. After this a central venous catheter was inserted but gas bubbles could not be aspirated. Arterial blood gas analysis showed a severe combined metabolic and respiratory acidosis and central venous pressure was 25 mm Hg. Fifteen minutes later, Sp_{O_2} dramatically increased to 100%. The operation was completed using an open approach with no major problems. Chest radiography performed in the operating room showed no obvious change, except for a slight enlargement of the cardiac shadow. The patient was transferred to the intensive care unit and recovered consciousness 10 h later. She was extubated 15 h later and had no sign of neurological deficit.

Discussion

Several causes for the cardiac arrest were possible, such as hypovolaemia, vagal reflex, or argon or carbon dioxide gas embolism. As the total infusion volume was 1750 ml of crystalloid, blood loss was only 100 g up to the occurrence of the cardiac arrest, urine output was more than 200 ml, and active bleeding was not seen we can more or less exclude the possibility of hypovolaemia. The abrupt increase in IAP to over 20 mm Hg induced by the ABC system could have reduced cardiac output secondary to an acute decrease in venous return. During light anaesthesia with the combination of general and epidural, a vagal reflex could occur. Sympathetic block by epidural anaesthesia could worsen cardiovascular decompensation during the head-up position. We cannot entirely exclude this possibility. A definitive diagnosis of an argon gas embolism requires the aspiration of gas bubbles and detection by transoesophageal Doppler. Argon could also accumulate in the peritoneal cavity, and the embolism could have been with a mixture of argon and carbon dioxide. However, the cardiac event occurred immediately after the use of the ABC system and a mill-wheel murmur was heard on auscultation. The most likely explanation for the cardiac arrest is that high-flow argon entered the opened hepatic vein when abdominal pressure was increased. Using an argon gas stream to form an ionized arc enhances electrosurgical coagulation. The jet flow of argon gas clears the bleeding away from the surgical field and allows coagulation of the surface under direct vision. However, argon can enter open blood vessels, with possibly fatal gas embolism. Although argon is physiologically inert, it is 17 times less soluble than carbon dioxide (0.029 *vs* 0.495 ml gas ml^{-1} blood).[4] For this reason, argon-rich emboli are not as readily absorbed and may pass into the systemic circulation. In an animal study, the number of venous gas bubbles depended on the gas flow rate, and the incidence of gas embolism increased when argon gas flow exceeded 12–15 litre min^{-1}.[5] Unfortunately, most laparoscopic insufflators do not regulate intra-abdominal pressure by actively venting excess gas from the peritoneal cavity, and they, therefore, cannot relieve increased pressure caused by the ABC system. Consequently, even if abdominal pressure increased above the insufflator's alarm limit, the ABC system would continue to supply argon. Although flow rates of 2–4 litre min^{-1} have been recommended for laparoscopic procedures,[2 6] we increased the gas flow to 6 litre min^{-1} because the surgeons could not control local bleeding at a gas flow of 4 ml min^{-1}. As a result, abdominal pressure exceeded 20 mmHg. In closed cavities, the ABC system acts as a secondary source of pressurized gas. We did not stop giving nitrous oxide when using the argon beam coagulator. Diffusion of nitrous oxide into the peritoneal cavity could increase the volume of gas and increase the intraperitoneal pressure even further. Manufacturers are already aware of the risk of gas embolism during laparoscopic use of ABC systems and provide specific instructions to minimize the associated risks. This is indicated by the following recommendations:[2 6] (1) the initial setting should be manual mode and the argon flow should be kept at the lowest level consistent with efficient system performance (i.e. 4 litre min^{-1} or less), (2) one instrument cannula vent should be left open to the atmosphere during the use of an ABC system and the electrode should be removed from the body cavity when ABC is not actually being performed, (3) only laparoscopic insufflators with non-defeatable audible and visual over-pressurization alarms should be used, and (4) the manufacturer's specific

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Assessment instruments used during anaesthetic simulation

Editor—We read with interest the article by Byrne and Greaves about the limits of assessment instruments used to measure educational outcomes in teaching and research in anaesthetic simulation.[1] We congratulate the authors for isolating a serious problem not only for anaesthesia education but also for other medical specialities. Medical education research and educational practice cannot advance without outcome measures that yield reliable and valid data. Such measures account for dependent variables in research and are needed to capture training results leading to focused feedback and improved performance among clinical trainees.

We also concur with the authors' conclusions that based on the studies reviewed, restricted to anaesthesia via the search strategy, '...the efficacy of methodologies for assessment of performance during simulation is largely undetermined.' Our purpose in this correspondence is to point out to readers that work on developing solid outcome measures for use in simulation-based research and education in another medical speciality—cardiology—is underway and has produced useful results. This letter describes our approach to measurement development and gives an example of how good outcome measures can contribute to a sustained programme of medical education research.

Our work has been addressed to clinical cardiology, especially student and resident acquisition of cardiology bedside skills. These skills include: measurement and interpretation of blood pressure; palpation of arterial pulses; inspection of jugular venous pulses; palpation of precordial impulses; auscultation in multiple areas; correlating these findings with underlying pathophysiology and diagnostic laboratory data; and addressing patient treatment and follow-up. Instruction and assessment of these bedside skills is accomplished using the 'Harvey' cardiology mannequin that can simulate 27 clinical conditions, and is linked to the UMedic multimedia computer system.[2]

The maximum utility of sophisticated mannequin and computer-based medical simulations is unfulfilled without the availability of measures of learning outcomes that yield reliable data. Given a reliable approach to learner evaluation, one can assess the teaching effectiveness of computer systems such as UMedic that include bedside skills such as those taught by 'Harvey'. We followed a rigorous eight-step development procedure to create reliable and valid multimedia computer-based measures of clinical cardiology skills. This approach is consistent with textbook descriptions of test construction methods[3,4] and approximates methods that have been used to develop reliable and valid attitude measures.[5,6]

The eight-step measurement development procedure we used is outlined below. A detailed description has been published elsewhere.[7]

1. *Specify the measurement domain,* (i.e. bedside skills in cardiology).
2. *Identify domain features,* (i.e. visual and auditory assessment of cardiac events at four levels of complexity, ranging from identifying a bedside finding to correlating a bedside finding with severity and necessity for treatment of the underlying disease process).
3. *Generate multimedia stems and five options.* Stems consist of the simulated patient's pertinent historical and clinical data in the form of computer graphics and digitized audio as well as video demonstrations of the bedside finding on 'Harvey'.
4. *Item review by external experts,* (i.e. peer review of the item pool for content, structure, appearance, consistency, and validity).
5. *Pilot test items using target population,* (i.e. administer items to a sample of students or residents to obtain response data and feedback about confusing or ambiguous item features).
6. *Revise items.* Each item was modified, if necessary, based on pilot test results and comments by students, residents, and local expert cardiologists.
7. *Administer items to a large group in the target population,* (i.e. obtain response data from a large sample of learners in the target population).
8. *Evaluate data via item and test analysis,* (i.e. assess responses the items produce among target learners, create equivalent pre- and post-tests, evaluate reliability).

Use of these procedures resulted in a set of 77 items which produced a reliability coefficient (KR 20) of 0.94 with an average per cent correct score of 71%. The average time per examination was 73 min. We subsequently identified content equivalent pre- and post-tests from the item pool. The 27 item pretest and 25 item post-test produced reliability coefficients (KR 20) of 0.81 and 0.84, respectively. Per cent correct for the two tests were 69.6% and 68.9%. Standard deviation and range for each test were also equivalent: 4.86 and 5–26 and 5.02 and 4–25, respectively. The total testing time for the pre- and post-tests was 29.6 and 28.2 min, respectively.

The availability of these systematically developed outcome measures has enabled our research group to conduct two cohort studies to evaluate the teaching effectiveness of 'Harvey' and UMedic for senior medical students and internal medicine residents.[8,9] Additional studies are being planned. We hope that this description of rigorous procedures for development of outcome measures for use in simulation-based medical education is informative for other investigators. We encourage medical education colleagues to create outcome measures 'by the book' to ensure that the data they yield are reliable and valid.

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1 Byrne AJ, Greaves JD. Assessment instruments used during anaesthetic simulation: review of published studies. *Br J Anaesth* 2001; **86**: 445–50
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Renal dysfunction following anaesthesia and surgery

Editor—We were interested to read Cittanova's Editorial on renal dysfunction following anaesthesia and surgery.[1] We agree that renal failure after any operation is an important and expensive complication that should be avoided if at all possible.[2] We take the view that minimizing renal failure after cardiac surgery is a cost-effective approach and in a new cardiac surgery service in Australia, we have achieved one of the lowest renal failure rates in the literature.[3] In this context, the alpha-2 agonist clonidine may have a valuable role in non-cardiac as well as cardiac surgery.[4,5] However, we would also agree that there must be standard definitions of renal dysfunction and renal failure to allow valid comparisons between institutions and populations.[3]

As to which measures of renal function are the most informative and easy to make, we would suggest use of cimetidine to block the tubular secretion of creatinine, thus using the relatively easy measurement of creatinine clearance to estimate glomerular filtration rate.[6] In fact, such measurements can be made as frequently as every 10 min provided there is accurate assessment of the urinary volume.[7,8] Other potentially useful, non-invasive and novel measures of renal function include duplex Doppler study of the interlobar arteries of the kidney and urinary oxygen tension.[6,9–11]

Uniform application of some, or all, of these methods for standardizing the assessment and measurement of pre- and postoperative renal dysfunction will help us achieve the goal of minimizing this dangerous and expensive complication of surgery and anaesthesia.

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1 Cittanova ML. Is perioperative renal dysfunction of no consequence? *Br J Anaesth* 2001; **86**: 164–6

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11 Tolley PM, Purcell A, Bolsin SN. Effect of i.v. furosemide on pelvic urinary oxygen tension in humans. *Br J Anaesth* 1999, **83**: 328–9

Editor—I was interested to read Dr Bolsin's remarks concerning my editorial.[1]

Indeed, cimetidine administration eliminates creatinine secretion thus improving the accuracy of creatinine clearance. The method can be proposed to limit the error in determining glomerular filtration rate (GFR). However, to date, the recommended dose of cimetidine remains unclear, ranging between 0.8 and 3.2 g, for a duration of 1–3 days[2] and the period of urine collection, which provides the accurate measurements is in fact 30–50 min.[1]

Concerning the use of the Doppler method, I do not agree with Dr Bolsin's comments on its accuracy to estimate renal function. This variable identifies a renal abnormality (i.e. decreased renal blood flow) but cannot be used to diagnose renal impairment. Since the definition of renal insufficiency is a decrease in GFR, definition of postoperative renal dysfunction should be based on GFR.

As stated by Tolley and colleagues,[3] oxygen tension may be an index of medullary blood flow. This variable is interesting but the relationship between medullary blood flow and GFR is complex, and includes autoregulation of GFR and normal control.[1] The two variables are linked, but no linear relationship exists between them.

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2 Mitch WE, MacKenzie W. Nutritional therapy in renal disease. In: Brenner BM, ed. *The Kidney*. Philadelphia: WB Saunders, 2000: 2299–340

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Perioperative bradycardia

Editor—Kinsella and Tuckey have filled an important gap in the anaesthetic literature with their comprehensive review of perioperative bradycardia and asystole,[1] but I would like to comment.

First, I was pleased that they repeated the advice of Greene and Brull,[2] emphasizing the necessity of using a slight head-down position during spinal-induced hypotension. In fact, it is my view that all patients who have received a central nerve block should be placed in that position to ensure venous return and maintain right atrial filling. Many anaesthetists seem to be concerned that the few degrees of head-down tilt that is needed will result in further cephalad spread of hyperbaric local anaesthetic solutions. However, such a modest tilt has little effect on intrathecal drug spread, yet it can have a crucial effect on venous return.

Second, I cannot agree with their interpretation of the report from Caplan and colleagues,[3] of 14 patients suffering a cardiac arrest during spinal anaesthesia which led to death or severe brain damage. Over 50% of these patients were actually noted to be cyanosed before the cardiac arrest, yet the assumption is that this was secondary to the acute circulatory change. I consider it at least possible that the cyanosis was an indication that the primary problem was hypoxia. These patients all had extensive blocks and were heavily sedated. De-afferentation and heavy sedation could well have led to ventilatory inadequacy and/or airway obstruction Developing hypoxaemia would not have been apparent from changes in vital signs because of the sympathetic nerve block preventing changes in pulse and blood pressure.

Because of their analysis of this report, Kinsella and Tuckey state that 'Hypnotic drugs should be given to obtain anxiolysis rather than deep sedation', and that 'The patient who is able to communicate symptoms may give an early warning of the development of a vasovagal reaction'. I must disagree Many patients are reluctant to accept a central nerve block if they are to be conscious during the operation, but are much happier if they are going to be asleep. There is no reason why such a request should be refused as long as the anaesthetist recognizes the importance of continuing to monitor the patient clinically as well as instrumentally. I would also guard against hoping that the patient will give early warning of the development of a vasovagal reaction. I have seen several that were remarkably rapid in onset.

Finally, I would draw attention again to the view that I have expressed previously in these pages regarding the importance of using sedative drugs to prevent vasovagal attacks during central nerve block.[4]

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1 Kinsella SM, Tuckey JP. Perioperative bradycardia and asystole: relationship to vasovagal syncope and the Bezold-Jarisch reflex. *Br J Anaesth* 2001; **86**: 859–68

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4 Burke D, Wildsmith JAW. Severe vasovagal attack during regional anaesthesia for caesarean section. *Br J Anaesth* 2000, **84**: 823–4

Editor—Thank you for the opportunity to respond to the letter from Professor Wildsmith. He makes points relating to the mechanism of bradycardia/asystole as discussed in the paper by Caplan and colleagues,[1] the management of patients having regional anaesthesia, and the treatment of vasovagal syncope.

When considering the closed claims analysis by Caplan and colleagues[1] of 14 cases of cardiac arrest during spinal anaesthesia, it is essential to distinguish between the precipitating factors that lead to reflex bradycardia, and the afferent pathways by which the reflex is induced. Caplan and colleagues' primary hypothesis was that unappreciated respiratory insufficiency was the cause of bradycardia/asystole. However, they were at a loss to explain half of the cases where deep sedation was not used, but did acknowledge that 'circulatory changes related to high sympathetic blockade may have played a role'. It is now clear that regional anaesthesia may cause bradycardia/asystole in the absence of sedation, as a result of reduced venous return Heavy sedation might rather reduce venous return through hypoxia and hypercapnoea, and therefore increase the risk. We think that it is more logical to acknowledge a baroreceptor/stretch receptor mechanism at work in all cases, augmented by the effects of hypoventilation, than to suggest (as does Professor Wildsmith) a chemoreflex bradycardia acting in some cases only. Furthermore, if a hypoxic chemoreflex is the cause, why did the bradycardia not respond to the positive pressure ventilation with 100% oxygen that was started within 1–4 min of detecting the first clue to problems?

We stand by our suggestion that the routine use of deep sedation during high regional anaesthesia is undesirable. A verbally unresponsive state was strongly linked to cyanosis being a presenting sign before bradycardia/arrest in Caplan and colleagues' series. We would again draw attention to the reduced doses of depressant drugs needed to produce sedation after high spinal anaesthesia is established.[2,3,4]

In our experience many patients are nervous firstly about the 'needle in the back', and secondly about feeling significant sensation or pain during the operation; once they are reassured that surgery is proceeding successfully they relax and start to enjoy the experience—or sometimes they have a true sleep, possibly aided by deafferentation.

The combination of general anaesthesia with high regional anaesthesia has not been identified as a risk for bradycardia/asystole, perhaps because of effective control of the airway and pulmonary ventilation, together with direct suppression of the reflexes.

We would agree with Professor Wildsmith about the judicious use of sedation to try and prevent vasovagal syncope during regional anaesthesia or general anaesthetic induction in patients with a known predisposition, as we stated. We would like to point out that the letter by Burke and Wildsmith[5] in fact refers to the use of thiopental to treat an established vasovagal episode rather than to prevent an attack. We are not aware of any literature on this and would welcome further reports of the suitability of this approach

However, although we may have some differences in approach from Professor Wildsmith, we are reassured that we agree on two crucial points: the imperative of ensuring venous return during high regional anaesthesia, and of continuous close perioperative monitoring.

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J P. Tuckey
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Management of purpura fulminans

Editor—I read with interest the case report by Nolan and Sinclair[1] discussing the management of the frustrating condition of purpura fulminans. I was interested to see that they list epidural analgesia as a possible therapeutic intervention for the treatment of digital gangrene. I would be interested to know their opinion on the following issues. Epidural analgesia has recently been shown to produce a 'steal phenomenon' in normal tissue surrounding free flaps, and in so doing aggravate graft ischaemia.[2] The vascular thrombosis and occlusion of the arterioles that occur in purpura fulminans could mimic some of the pathophysiology that occurs in free grafts and so epidural analgesics could make the condition worse, not better. Added to this is the fact that coexisting thrombocytopenia, heparin therapy, and coagulopathy are all strongly associated with an increased risk of spinal canal haematoma formation.[3] With these considerations in mind, do the authors not feel that epidural analgesia should be contraindicated until these issues have been fully investigated?

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Editor—We are glad that our article on purpura fulminans has created interest.

We acknowledge the concern that has been expressed by readers regarding a 'steal phenomenon' that occurs surrounding free flaps when epidural analgesia is used. However, there are many studies that have documented improved skin and lower limb blood flow after lumbar epidural,[1–3] which we feel would justify advocating the use of such techniques in the condition we describe.

We stated in our paper that there is obviously a risk of spinal canal haematoma formation in the presence of an associated coagulopathy and, in such cases, we feel regional techniques should certainly be avoided. We accept that there is limited evidence for a number of treatments that are used in purpura fulminans. However, for a condition that is so disabling, should we avoid giving these treatments just because they have not been proven beyond doubt?

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Undiagnosed myasthenia gravis unmasked by neuromuscular blockade

Editor—We read with interest the article by Dunsire and coworkers.[1] In the final section of this paper the authors state that manual evaluation of double burst stimulation (DBS) is the best and safest monitoring technique to avoid unrecognized postoperative residual neuromuscular block. This statement is misleading and, according to currently available data, incorrect. Previous studies by Fruergaard[2] and Ueda[3] investigated the effectiveness of manual evaluation of DBS monitoring to prevent unrecognized residual block. In these studies, the incidence of unrecognized block was up to 24% using DBS. These data clearly show that manual evaluation of DBS is insufficient. In contrast, Mortensen and colleagues[4] were able to demonstrate that accelerography is an excellent neuromuscular monitoring technique to avoid undetected residual block (TOF-Guard, TOF-Watch). In their study,[4] none of the patients monitored by accelerography had undetected residual block.

In contrast to the questionable and, in our view, incorrect statement of Dunsire and colleagues,[1] that all other techniques than manual evaluation of DBS are expensive and impracticable, we wish to point out that accelerography is easy to perform in the operation room; it is a small piece of equipment, and it is not expensive (around 500 Euro). Furthermore, it can be set up and started at any time during anaesthesia (e.g. at the end of surgery or in problem situations during anaesthesia). There is no need for any zero-calibration before administration of a muscle relaxant. In our institution, we were able to equip every anaesthetic area with an accelerograph. We believe that this should be possible in any institution, especially if one considers that the costs of treating pulmonary complications, which do occur quite frequently in the presence of undetected residual neuromuscular block,[5] exceed the costs of one accelerograph.

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Editor—Thank you for the opportunity to reply to the issues raised by Puhringer and colleagues regarding our paper.[1]

First, we did not state that 'manual evaluation of double burst stimulation (DBS) is the best and safest monitoring technique to avoid unrecognized postoperative neuromuscular blockade'. What we stated was 'perhaps the simplest way to avoid postoperative residual curarization is to monitor all patients who receive neuromuscular blockers with DBS at regular intervals throughout anaesthesia'. There is clearly a world of difference between the two statements.

Whilst the findings of Fruergaard[2] and Ueda[3] indicate an incidence of residual neuromuscular blockade of up to 24% after manual evaluation of DBS, we would like to raise a couple of issues with regard to these studies. First, the long acting agent, pancuronium was used as the neuromuscular blocking agent. This drug is almost obsolete in UK anaesthetic practice. Second, in the study by Ueda[3] the dose of neostigmine used to 'reverse' block was only 1.5 mg and not the more commonly used dose of 2.5 mg. Perhaps if 2.5 mg had been used, the residual block rate would have dropped from 6.7%? Nevertheless there are several studies[4 5] available that demonstrate residual muscular block with intermediate acting neuromuscular blockers, indicating that it is also a problem with these newer drugs. Use of DBS to assess the degree of residual block with intermediate acting drugs increases the sensitivity of the assessment but does not guarantee that full recovery from block has occurred.[6 7] Absence of visible fade in the DBS does not mean that the train-of-four ratio (TOF) will be greater than 0.7. Using DBS as a monitor of neuromuscular function diminishes the chance of residual block but does not eliminate it.

We agree that objective methods of measurement are superior to subjective ones and that the paper by Mortenson[8] provides good evidence that accelerography can help to avoid residual neuromuscular blockade. Its use abolishes the subjective element of the assessment and allows direct measurement. It also provides a 'written' record of the TOF ratio throughout the procedure.

We accept we were a little over zealous in our criticism of accelerography as it is neither expensive nor impractical. It appears to be assuming a greater role in UK anaesthetic practice with the availability of the TOF guard.

With regard to our original statement 'the simplest way to avoid postoperative residual curarization is to monitor all patients who receive neuromuscular blockers with DBS at regular intervals throughout anaesthesia'; this was implied when the choice of neuromuscular monitoring lay between TOF and DBS.

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Book Reviews

Cardiac Anesthesia 2nd Edn. F.G. Estafanous, P.G. Barash and J.G. Reves (editors). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 1035; indexed; illustrated. Price US$195. ISBN 0-7817-2195-4.

Cardiac Anesthesia aims to provide a detailed reference foundation for those involved in providing cardiothoracic anaesthesia. Sixty authors have contributed to this textbook. All except two of the authors work in the USA or Canada and many are eminent in cardiothoracic research. As with all books written by multiple authors, there is variation in style and in the quality of the information between the chapters. Overall, the editing process has been good; there is very little duplication of information. Equally good is the proof reading which has resulted in very few typing errors, and the readability. This is a second edition. Some chapters are well updated and referenced, but for others I doubted that the literature had been reviewed again in any detail. The most recent references throughout are from 1999, simply reflecting the inevitable time lag between writing the chapters and their publication.

The book is divided into seven parts. The first part includes excellent chapters on the history of cardiac surgery and anaesthesia and cardiac pharmacology as well as two other good ones: one on the management of arrhythmias and one on cardiac catheterization. I was disappointed with the chapter on cardiovascular physiology; it was fundamental physiology textbook information and far too basic for its readers, many of whom have day-to-day experience of manipulating the circulation. Important omissions are information on right ventricular function and the physiology of the pulmonary circulation.

The second part, general considerations, includes preoperative assessment, patient monitoring, and cardiovascular pharmacology of anaesthetic agents, none of which have been particularly well updated; they contain rather old references and there were omissions of recent developments in these areas. The new chapter on echocardiography was excellent with clear explanation such that a novice could understand the subject. However, some abbreviations used in the equations were not always clearly defined. There are two pages of colour illustrations relating to echocardiography that, unfortunately, have been placed in the centre of the book, widely separate from this chapter and coming within a chapter on valvular heart disease. I presume they have been placed there for some publishing reason as they are the only colour prints in the book and are not page numbered.

Part three, chapters that consider aspects of cardiopulmonary bypass, is generally of a high standard and includes an excellent and important new chapter on brain injury and brain protection. The chapter on separation from cardiopulmonary bypass, however, is to my mind prescriptive, relies heavily on personal and institutional experience, and presents too little evidence-based information. It lacks a balanced evaluation of inotropic drugs and omits any mention of the calcium sensitizers that are currently undergoing development.

Part four focuses on intensive care issues, both paediatric and adult. I thought that the chapter on adult intensive care was simplistic, but that may reflect different practice between North America and the UK. It concentrates on early postoperative complications, but there is little or no comment on the management of acute respiratory distress, or severe renal or haptic dysfunction, all of which are problems that beset the long-term occupants of my unit.

Part five is the largest section and covers special topics. I particularly enjoyed the chapters on valvular heart disease, surgical and device therapy for cardiac arrhythmia, minimally invasive cardiac surgery, and anaesthesia for thoracic aortic surgery; all are well structured, clear, excellent chapters. I was very disappointed with the chapter on anaesthesia for coronary artery bypass surgery; this large and most well-researched part of cardiac anaesthetic practice was superficially covered in a mere 12 pages of text. I could not understand why there was a chapter entitled 'Anesthesia for Pulmonary and Mediastinal Surgery' in this book on cardiac anaesthesia. Surely thoracic anaesthesia is large enough for a separate textbook; this single chapter is inadequate. By the same token the chapters in part six, on cardiac patients undergoing non-cardiac operations would be more appropriate in a general textbook of anaesthesia. The final part on audit, quality of, and education in cardiac anaesthesia is both interesting and thought provoking. There are some topics that have been barely touched upon, or that could have been more fully explained. Amongst these are intra-aortic balloon counter pulsation, myocardial hibernation, myocardial stunning, ischaemic preconditioning and fast track recovery

This will be a useful textbook for anaesthetists in training and for those who wish to pursue cardiac anaesthesia as a specialist interest. It is sufficiently detailed, not too large, and readable. Most consultants practising cardiac anaesthesia will find it less useful mainly because some of the new and exciting concepts and research relating to cardiac anaesthesia and surgery have been inadequately covered.

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The Complete Recovery Room Book. 3rd Edn. A. Hatfield and M. Tronson. Published by Oxford University Press, Oxford. Pp. 586; indexed; illustrated. Price £32.50. ISBN 019 263 2183.

This book, now in its third edition, was written for those 'who are neither fully trained anaesthetists, nor specialist trained recovery room nursing staff'. It was intended to be a reference book and a practical guide to the management of patients in the immediate postoperative period. The previous editions were specifically aimed at those working in isolated hospitals. The preface to the third edition outlines recent changes in surgical practice, emphasizes the importance of prompt treatment of complications in the prevention of subsequent morbidity, and suggests, rightly, that recovery room care should become a recognized speciality in the future.

There are 25 chapters and eight appendices. The contents range from routine recovery room procedures, through to the design, staffing and management of recovery rooms. There are chapters on every aspect of care, including surgical and anaesthetic complications, pain relief, nausea and vomiting, cardiac, respiratory and neurophysiology, pharmacology, and descriptions of a variety of the more common medical conditions. It is, as the authors suggest, encyclopaedic, didactic, and not intended to be read at one sitting.

The authors have created some difficulties for themselves in deliberately setting out to write a book that is intended for both anaesthetists and nurses. Compromise is inevitable. Most of the time, instructions are clearly addressed to the recovery nurse and undoubtedly it is an excellent text for nurses specializing in recovery room care. However, many of the treatments and procedures described would normally only be undertaken by

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doctors, although there are places in which the dividing line is not always clear. Whilst anaesthetists in their early training would find it worthwhile to read some chapters, they could be irritated by the chatty nature of the writing and the simplistic explanations. Whilst trainees might occasionally use it as a reference book in the recovery room, I cannot imagine them wanting to own personal copies.

Despite these reservations, I found most of the advice sensible and practical. The authors have given clear accounts of recovery room care and I am pleased to donate my copy to the recovery room. I envy the standards that the authors have achieved and only wish that we had recovery bays for three times the number of operating theatres and could nurse tonsillectomies for at least 90 min, as they recommend.

The layout is imaginative and the book is easy to read. The aphorisms are helpful. There are a number of figures and diagrams, some of which contain guidelines and protocols that could be adapted for wall charts. There are useful appendices, which include information on infusions, arrhythmias, numerical data and emergency trolleys

Unfortunately, my enthusiasm for this book was tempered by the large number of typographical/spelling mistakes, present in both the text and the reference journal titles. Many of these could have been avoided by the use of a spell-checking programme. The remainder should have been corrected by careful proofreading. I am surprised that an experienced publisher such as Oxford University Press could have released a book with so many errors. These should be corrected at the next printing.

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Web site review. www.capnography.com K.B. Shankar.

To review a web site offers a different challenge from a book. A book is permanent, can be read anywhere, and annotated. It offers all readers the same experience. A web site, in contrast, can be updated by the author at any time, or even destroyed completely. It can be accessed only by those with specialized equipment, and what the reader sees depends in part upon their particular hardware and web browser. A web site is virtually free to the user, but of course anyone can publish anything on the web, without any peer review. Yet a web publisher can reach a potentially vast readership, and has the opportunity to create something quite different from a book, with the possibilities of animation and of interaction.

This web site, the work of Professor Shankar, was accessed at the first attempt, using a PC with an Intel Celeron Processor, running at 366 MHz, fitted with a 57.6 kbaud modem, and running Microsoft Internet Explorer, version 5.

The main home page has a left-hand panel of shortcuts to other parts of the site, but is dominated by the right-hand panel, topped by an animated title. There are no fewer than five other animated panels on the main home page, all of capnogram tracings showing, for example, the effect of apnoea, bronchospasm and re-breathing.

The home page sets the scene for the site, which makes extensive use of animated graphics. For example, the page of ASA standards of monitoring during anaesthesia shows the elements of patient monitoring, arranged around a graphic of the cardiorespiratory system of a patient, in which oxygen is inhaled and circulates to the brain where carbon dioxide is produced, subsequently exhaled, and monitored.

There is a lot of material on this site, and it is impossible to list all the good things. The physiology section has nine pages of considerable depth. The coverage here is serious and backed by substantial lists of references. There is a discussion of the size and causes of end-tidal arterial gradients in $P\text{CO}_2$ There are clinical sections on capnography in paediatrics, thoracic anaesthesia, and laparoscopy. There is an extensive encyclopaedia of capnograms, with tracings showing the effects of clinical abnormalities and of various categories of equipment malfunction. There is also a page where several capnograms are arranged by name around a central screen. Placing the mouse cursor over the capnogram title brings up the relevant tracing on the central screen.

It would be unfair to dwell on the possible shortcomings of this site. The use of colour is a little garish; and there are problems with text formatting after subscripts. There is also a tendency to slip into 'McDonalds' speak', with sections on 'capno-tips', 'capno-questions', and even 'capno-pitfalls'.

So what does this web site provide? Certainly it provides fun. It will be a learning resource for students—and I will be recommending it. It may become a forum for specialists, as its author hopes, but on this only time will tell. The main obstacle to the usefulness of this site as a source of reference for the practitioner is simply one of awareness. The anaesthetist about to undertake a thoracoscopy, for example, would find useful material here, but is still more likely to look at a textbook or do a Medline search.

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Critical Care Focus 6. Cardiology in Critical Illness. Helen F. Galley (editor). Published by BMJ Books, London Pp. 60, indexed. Price £14.95. ISBN 0-7279-1543-6.

This is the sixth book in the *Critical Care Focus* series. The objectives of this series are to provide a concise account of current practice and opinion from experts in the field. Without doubt, *Cardiology in Critical Illness* achieves these aims.

Each chapter is based on a presentation by a different author from a cardiology, surgical, or anaesthesia and intensive care background, and focuses on a single topic. Consequently, the differing styles and approaches not only make the book eminently readable but also broaden its relevance to an extensive audience. Professors Ball and Hampton provide an insight into the pathophysiology and treatment of heart failure respectively. These two chapters are not only of interest to those directly concerned with the care of the critically ill, but also provide useful information for anaesthetists and surgeons involved in the perioperative optimization of patients with heart failure. Any trainee reading Dr Montgomery's chapter 'Managing Arrhythmias', will find themselves armed with a robust approach to arrhythmias in the critically ill and, importantly, the logic behind that approach. In the section on 'How to Use Echocardiography', I was reminded of the potential of echocardiography in the critically ill and the importance of asking the right questions of the operator. Professor Parrillo's account of the vasculature in sepsis and septic shock is of interest to any clinician involved in the care of such patients. The reader is provided with up-to-date information on left ventricular assist devices and also, perhaps, a glimpse into the future in the chapter on 'Artificial Hearts'. The didactic description of 'Estimation of Cardiac Output' is particularly useful reading for examination candidates. The high incidence of coronary artery disease in all our practices makes Professor Crossman's contribution relevant to most healthcare professionals.

This little book is not a comprehensive textbook or practical handbook. It will, however, stimulate the interest of most readers in at least one of the areas covered, and encourage further reading The editor, editorial board and contributors are to be congratulated on producing a readable, well-indexed book with some relevance to all healthcare professionals involved in critical care.

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ABSTRACTS

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*(The name of the presenting author is shown in bold type. *Indicates non-member. All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review)*

VERBAL PRESENTATIONS

Learning during surgery

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Although learning during anaesthesia has been demonstrated,[1] there is little consistency in findings across studies. One intriguing suggestion is that surgery appears to facilitate learning.[2] Clinical studies using patients have found learning[3] whereas attempts to replicate these findings in volunteers using lower doses of anaesthetic have been unsuccessful.[4] We tested the prediction that surgery would facilitate learning. Sixty-four patients (35 male, 29 female; mean age 42 yr) were recruited. All patients were ASA physical status 1 undergoing day surgery.

Patients received a standardized anaesthetic consisting of fentanyl 1.5 µg kg^{-1} and then propofol target controlled infusion ranging from 4.53 to 8.54 µg ml^{-1}. Patients breathed 66% nitrous oxide and 33% oxygen spontaneously through a laryngeal mask.

Each patient was assigned randomly to preoperative or intraoperative word presentation. Preoperative word presentation took place after induction and once anaesthetic maintenance was commenced; intraoperative presentation started upon first surgical incision. Word presentation comprised an auditory list of 14 words, during which BIS and anaesthetic variables were recorded at 1 min intervals. Implicit and explicit memory were tested on recovery by word stem completion and recognition tests, respectively (Table 1).

No patient had spontaneous recollection of surgical events. Patients in the intraoperative study group responded significantly above baseline on the implicit memory test. In contrast, the preoperative study group did not perform above baseline. Mean BIS did not differ between groups. We conclude that surgery may facilitate learning during anaesthesia.

Keywords: memory; anaesthesia

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Making explicit anaesthetic expertise: methodological consideration and subjects' perceptions

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Knowledge in anaesthesia, as in other practical fields, involves two manifestations: the *explicit*, public knowledge found in textbooks and journals and the *tacit*, personal knowledge gained from experience. Shifts towards competency-based training in anaesthesia risk losing sight of the tacit aspects of anaesthetic knowledge,[1] as they cannot be quantified or standardized.

Table 1 Mean anaesthetic measurements during stimulus presentation and postoperative implicit and explicit memory scores for preoperative and intraoperative study groups; *95% Confidence Interval

	Surgery duration (min)	BIS	Pulse	Mean BP	E'_{CO_2} kPa	RR	TCI µg ml^{-1}	Implicit memory mean (CI)*	Explicit memory mean (CI)*
Pre	31	39.8	66	69	6 8	9	5.2	0 02 (–0 04 to 0.1)	0.01 (–0 03 to 0 06)
Intra	36	43 6	72	75	6 7	15	5.8	0 08 (0 01 to 0.15)	0.00 (–0 02 to 0.03)

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The study was designed to explore these two facets of knowledge by studying anaesthetic work in natural (rather than experimental) settings.[2] Two approaches were used. First, anaesthetists were observed at work in theatre, by an 'insider' (former anaesthetic nurse) and 'outsiders' (sociologists). The field notes were then transcribed and the text analysed for recurring themes, phrases, and patterns of behaviour. Where possible, debriefing interviews were conducted after the observation. Second, we conducted semi-structured interviews with anaesthetists, operating department practitioners, and recovery nurses, allowing us to explore the previously identified themes in more detail. We are also using these to seek participants' views about being observed and researched in this way.

None of our participating staff had ever been the subject of research. Some were initially reluctant to be observed, but none refused. To date, 25 anaesthetists (at various grades) have been observed and 16 anaesthetic staff (medical, nursing, and support) have been interviewed. Some of the richest data have been provided by observing trainee anaesthetists at work, but there are particular issues in dealing with these data, which touch on the role of the research, the relationship between the research subjects and the research team and confidentiality. We spent considerable time before the study started ensuring that anaesthetists knew the research team and understood the aims of the study. Possible concerns about the use of the data were assuaged by anonymizing transcripts and frequent feeding back of findings at open 'data workshops' and through individual debriefing. To date the anaesthetists have related positively to feedback about the emerging themes.

These research methods are valid and have long been used in other fields. The use of insider and outsider researchers has not caused problems, and there have been few discordant interpretations of the data. Nonetheless some methodological issues remain unresolved. What is the impact of observation on what is being observed? How far can the findings from this single group of practitioners be applied to others? How should the analysis deal with discrepancies between interview accounts ('post hoc' rationalizations) and observational data, particularly as tacit knowledge, by definition, cannot easily be articulated.

Acknowledgements: We would like to thank all participating staff. The study 'The problem of expertise in anaesthesia' is funded by the North West Regional R&D Fund (RDO/28/3/05).

Keywords: anaesthesia, competence; research, qualitative

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Clinically relevent concentrations of propfol for *in vitro* studies

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It is often assumed that results obtained in *in vitro* studies will have some clinical relevance if the perfusing concentration is close to the concentration observed in blood *in vivo*. A heart tissue:blood propofol concentration ratio close to unity has been noted *in vivo* in rats[1] but tissue:organ bath ratios have not been measured. This study was designed to measure the uptake of propofol by the isolated rat heart *in vitro* from buffered aqueous solution and to study the effect of serum albumin on this uptake.

Table 2 Mean (SD) propofol concentrations ($\mu g\,ml^{-1}$ or $mg\,g^{-1}$) and partition coefficient (λ) after 75 min equilibration n=6; *P<0.001 *vs* propofol ; **P<0.001 *vs* 2% BSA

	Propofol	Propofol+2% BSA	Propofol+4% BSA
Reservoir	5.09 (2.21)	5.30 (1.34)	7.64 (2.43)
Aortic cannula	3.66 (2.81)	3.73 (1.27)	6.85 (2.57)
Outflow	3.58 (2.19)	3.57 (1.43)	6.82 (2.16)
Heart tissue	93.66 (26.15)	48.68 (8.05)*	27.41 (6.96)*, **
λ Heart/Outflow	37.1 (11.2)	16.9 (10.2)*	4.5 (2.2)*, **

Hearts were obtained from female Wistar rats killed by stunning and exsanguination. The heart was mounted in a Langendorff apparatus and perfused at 37°C with Krebs–Henseleit (KH) solution with propofol 10 mg ml^{-1} (group 1), propofol 10 mg ml^{-1}+bovine serum albumin (BSA) 2% (group 2), propofol 10 mg ml^{-1}+BSA 4% (group 3) or intralipid. Samples of perfusate were collected from the reservoir, the cannula as it entered the aorta, and at the outflow from the glass chamber. Samples were taken before and 5, 15, 30, 45, 60, and 75 min after switching to a test perfusate. After 75 min, the hearts were removed, weighed and frozen at –20°C until analysis for propofol concentration by high performance liquid chromatography.[2]

Propofol concentrations in heart tissue perfused with the addition of BSA were significantly lower than those perfused with propofol alone (Table 2). After 75 min equilibration the propofol concentration in outflow perfusate was reduced to 40–70% of the nominal concentration. Heart/outflow partition coefficients were greatly influenced by the addition of BSA. These results indicate that, in the absence of added protein in *in vitro* test systems, propofol perfusate concentrations, equivalent to plasma concentrations in man, may achieve tissue propofol concentrations greatly in excess of tissue concentrations resulting from equilibration between blood and tissues *in vivo*.

Acknowledgements: This study was financed with a research grant from AstraZeneca.

Keywords: anaesthetics i.v., propofol; model, *in vitro* validation

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Effect of intubation with and without opioids on the subcortical somatosensory evoked response

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Evoked responses usually decrease with increasing anaesthetic depth, and increase with noxious stimuli. These changes are obtunded by opioids. Previous work using desflurane, sevoflurane, and propofol at steady state concentrations has revealed an increase in P_{15}-N_{20} amplitude with increasing anaesthetic depth.[1 2] Using intubation as a reproducible stimulus, we have investigated its effect on the P_{15}-N_{20}, N_{20}-P_{25} and P_{25}-N_{35} amplitudes of the somatosensory evoked response (SER). These amplitudes represent activity in the pons/thalamus, thalamus/primary sensory cortex, and sensory cortex, respectively.[3]

Eighteen patients aged 27–71 yr were recruited. After induction with sevoflurane in oxygen, vecuronium 0.1 mg kg^{-1} was given and the subjects were ventilated to normocapnoea via a laryngeal mask airway.† After 20 min of anaesthesia maintained at 3% sevoflurane end-tidal, the subjects were randomized to receive alfentanil 50 µg kg^{-1} or saline as a bolus, and intubated 60 s later. The median nerve was stimulated at the wrist with an electrical pulse delivered at a rate of 2.2 s^{-1}, and at intensity above the motor threshold. The SER was derived from the electroencephalogram (EEG) and recorded using electrodes at Fz and C$_3$. SER data corresponding to 2.6 min blocks at steady state and immediately after intubation (356 EEG sweeps) were log transformed and analysed offline

In the saline group, intubation caused a significant decrease in the P$_{15}$-N$_{20}$ (P<0.005) and N$_{20}$-P$_{25}$ (P<0.05) amplitudes. This response to intubation was greatly decreased in the SER data from the alfentanil subjects, although the trend remained (see Table 3). The difference between groups (effect of the alfentanil bolus) was significant for the P$_{15}$-N$_{20}$ amplitude only (P<0.05).

Table 3 SER amplitude changes with intubation (data where P<0.05 are indicated, *)

Percentage change	P$_{15}$-N$_{20}$	N$_{20}$-P$_{25}$	P$_{25}$-N$_{35}$
Saline			
Mean	–44*	–33*	–16
95% CI	–25 to –58	–7 to –52	57 to –67
Alfentanil			
Mean	–12	–12	2
95% CI	0 to –23	7 to –28	79 to –42

We have shown that the increase in P$_{15}$-N$_{20}$ amplitude with increasing sevoflurane concentration previously reported[1] is reversible with stimulation: intubation produces a significant decrease in amplitude. Thus, this response appears to behave in a reversed manner to other evoked responses at the subcortical level. High dose alfentanil decreases the SER amplitude changes caused by intubation at both cortical and subcortical levels.

Keywords: brain, evoked responses; intubation tracheal, responses

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The pressor responses to the three phases of nasotracheal intubation

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Nasotracheal intubation is an effective way to secure the airway in patients undergoing maxillofacial surgery, but it is associated with a more profound pressor response than orotracheal intubation.[1] Nasotracheal intubation involves three phases. (1) The tracheal tube is inserted through the nostril and into the pharynx. (2) Direct laryngoscopy is performed. (3) The tracheal tube is passed through the larynx and into the trachea. The objective of this study was to determine how the three phases of nasotracheal intubation contributed to the haemodynamic response.

Sixty ASA I–II patients, aged 16–65 yr, undergoing elective maxillofacial surgery, were studied. They were given a standard general anaesthetic comprising fentanyl, propofol, atracurium, isoflurane 0.5% (end-tidal) in 66% nitrous oxide and 33% oxygen, and then randomized into three groups. In group 1, a shortened nasotracheal tube was inserted through the nostril and into the pharynx. In group 2, a shortened tube was inserted and direct laryngoscopy was performed. In group 3, full nasotracheal intubation was performed. Heart rate and indirect arterial pressure were measured 30 s after the manoeuvre and then every minute for a further 3 min. Data were analysed using one-way ANOVA and Student's t-tests with Bonferroni corrections.

The three groups were similar in age, weight, and sex. There was a significant pressor response in all three groups (Table 4). The increase in heart rate and mean arterial pressure (MAP) in group 3 was significantly greater than in groups 1 and 2. The differences between the increases in heart rate and MAP in groups 1 and 2 did not achieve statistical significance, however, the increase in MAP in group 2 was sustained for a longer period.

Nasopharyngeal intubation alone causes significant hypertension and this may account for the greater pressor response to nasotracheal compared with orotracheal intubation. It is conceivable that this response may be amenable to attenuation by topical anaesthesia of the nasopharyngeal mucosa Nasopharyngeal intubation with or without direct laryngoscopy does not significantly increase the heart rate. One possible explanation for this is the nasocardiac reflex. The placement of the tracheal tube through the larynx and into the trachea results in a significant further increase in arterial pressure and heart rate.

Keywords intubation nasotracheal; complications, cardiovascular response

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Table 4 Data expressed as mean (SD). $^{*}P$<0.05 within group. $^{\#\S}P$<0.05 between groups

	Group 1	Group 2	Group 3
Maximum increase in heart rate (min $^{-1}$)	0.6 (6.5)$^{\#}$	2.1 (7.6)§	17.6 (13.6)$^{*,\#,\S}$
Maximum increase in MAP (mm Hg)	27.2 (13.3)$^{*,\#}$	31.9 (11.7)*,§	44.9 (13.2)$^{*,\#,\S}$

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†LMA is the property of Intravent Limited

Prophylaxis of nausea and vomiting after spinal morphine analgesia for Caesarean section: comparison between cyclizine, dexamethasone, and placebo

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Low dose intrathecal (spinal) morphine (0.1–0.2 mg) for Caesarean section delivers excellent analgesia but is associated with significant postoperative nausea and vomiting (PONV).[1] A recent study has shown an antiemetic effect of dexamethasone after epidural morphine for Caesarean section.[2] We have evaluated the antiemetic efficacy of cyclizine and dexamethasone compared with placebo in women receiving spinal morphine analgesia for Caesarean section.

Ninety women undergoing elective Caesarean section under spinal anaesthesia were allocated randomly, in a double-blind study design, to receive either cyclizine 50 mg, dexamethasone 8 mg, or placebo as an infusion in 100 ml 0.9% saline on completion of surgery. Spinal anaesthesia was administered at L3-4 or L4-5 intervertebral space with a Whitacre 26G needle using 0.5% hyperbaric bupivacaine 2.0 ml, fentanyl 10 µg, and spinal morphine 0.2 mg. Outcome measures (documented at 3, 6, 12, and 24 h postoperatively by investigators blind to the group allocation) were incidence of nausea and vomiting, requirement for rescue antiemetic medication, severity of nausea on a four-point categorical scale, number of vomiting episodes, and adverse effects. After inspection for distribution, normally distributed variables were compared using ANOVA with post hoc Dunnet's test. Categorical data were compared using chi-squared analysis of contingency tables on SPSS v9.

Severity scores for nausea and vomiting episodes were significantly less in patients receiving cyclizine compared with both dexamethasone and placebo at 3 h and placebo only at 6 h ($P<0.05$ each comparison), but not at 12 or 24 h.

There were no significant differences in pain, pruritus, sedation, arterial pressure, or respiratory rate Overall satisfaction with antiemetic therapy at 24 h, expressed on a 100 mm visual analogue scale, was higher in cyclizine than either dexamethasone or placebo groups (78 (28) *vs* 58 (31) and 51 (28), $P=0.03$ and $P=0.008$, respectively) (Table 5).

We conclude that cyclizine, compared with dexamethasone or placebo, reduces the overall incidence of nausea, vomiting and need for supplementary antiemetic therapy and also the severity of nausea and number of vomiting episodes in the early postoperative period, after 0.2 mg spinal morphine analgesia for Caesarean section.

Keywords: analgesics opioid, morphine; complications, nausea and vomiting

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Effect of saline volume used to identify the epidural space during CSE anaesthesia for Caesarean section

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Epidural volume may influence the spread of spinal anaesthesia. After epidural analgesia in labour, intrathecal injection of bupivacaine 10 mg has produced total spinal anaesthesia [1] Likewise, epidural saline injection increases block height after spinal injection of bupivacaine.[2] We have previously demonstrated that the Oxford position confers more predictable control of cephalad spread of spinal block.[3] However, it has been our impression that when performing CSE anaesthesia in the Oxford position, larger saline volumes used to identify the epidural space produced more rapid spread of block. We, therefore, examined the effects of different saline volumes used as part of a CSE technique on subsequent spinal block.

We studied 90 women (aged 23–41 yr) undergoing elective Caesarean section. They were randomized to receive 2, 5, or 10 ml saline to identify the epidural space during needle through needle CSE anaesthesia using the Oxford position. Intravenous fluid preload of 15 ml kg^{-1} Hartmann's solution was given before identification of the epidural space and intrathecal injection of hyperbaric bupivacaine 12.5 mg with fentanyl 12.5 µg. Arterial pressure (AP) was recorded at 1-min intervals until delivery Ephedrine 6 mg was given on each occasion AP fell below 80% of baseline. Block height was tested every 3 min using light touch with T5 deemed adequate for surgery Neonates were assessed by Apgar scores and cord gases. Data were analysed using ANOVA with $P<0.05$ considered significant.

Table 5 Incidence of nausea, vomiting, and rescue antiemetic therapy at any time during the study

	Cyclizine (C) (*n*=30)	**Dexamethasone (D) (*n*=30)**	**Placebo (P) (*n*=30)**	***P* value**
Nausea at any time, *n* (%)	10 (33)	18 (60)	20 (67)	*P*=0.02, C *vs* P, *P*=0.04, C *vs* D
Vomiting at any time, *n* (%)	9 (30)	17 (57)	18 (60)	*P*=0.03, C *vs* P, *P*=0.04, C *vs* D
Rescue antiemetic at any time, *n* (%)	4 (13)	17 (57)	19 (63)	*P*=0.0001, C *vs* P, *P*=0.001, C *vs* D

Table 6 Onset of anaesthesia, ephedrine requirement and cord gas analysis. Data are mean (SEM) *$P=0.009$ compared with 5 ml *$P=0.013$ compared with 5 ml

	2 ml (*n*=29)	**5 ml (*n*=29)**	**10 ml (*n*=28)**	***P* value**
Time to T5 (min)	16.7 (1.1)	18.8 (2.1)	17.4 (2.0)	0.399
Ephedrine required (mg)	21.4 (2.8)	18.9 (3.2)	29.4 (4.2)*	0.009
Arterial pH	7.264 (0.009)	7.275 (0.008)	7.228 (0.015)**	0.013
Venous pH	7.330 (0.007)	7.325 (0.006)	7.311 (0.008)	0.136

No significant differences were found between groups in maternal characteristics, performance of CSE, need for epidural supplements, treatment of nausea and vomiting, and timing of postoperative analgesia. No block extended above T2 was recorded before skin incision. Data on spread of anaesthesia, ephedrine requirement, and cord gas analysis are shown in Table 6.

Excessive upper block height is unlikely when using the Oxford position regardless of saline volume. Using saline 10 ml to identify the epidural space did not produce more rapid spread of block. However, its use was associated with greater ephedrine requirement and deterioration in arterial, but not venous, cord gas values. Smaller saline volumes are, therefore, preferable when performing CSE anaesthesia in the Oxford position.

Keywords: anaesthetic techniques, epidural; anaesthetic techniques, subarchnoid

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Comparison of thresholds for giving phenylephrine during spinal anaesthesia for Caesarean section

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Maternal hypotension is an important complication of spinal anaesthesia for Caesarean section. Mean umbilical artery pH (UApH) at delivery is higher if maternal hypotension is prevented by giving ephedrine promptly.[1] The aim of this study was to compare two thresholds for giving phenylephrine and to examine the effect on umbilical artery pH at delivery.

Thirty-two healthy women with an uncomplicated singleton pregnancy scheduled for elective Caesarean section were recruited. Baseline maternal systolic arterial pressure (SAP) and heart rate were measured before spinal anaesthesia.[2] Patients were allocated randomly to be given phenylephrine 100 µg intravenously whenever SAP had decreased to either 95% of baseline (group A) or 80% of baseline (group B). The anaesthetists were blinded to patient allocation. Arterial pressure was measured at 1 min intervals after induction of spinal anaesthesia. Atropine 0.6 mg was given if maternal heart rate fell by 25% from its baseline. A sample of arterial blood was taken from a double-clamped section of umbilical cord immediately after delivery of the baby. The UApH was measured within 5 min.

One patient was withdrawn because the uterine incision to delivery (UD) interval was 540 s. A second patient was withdrawn because inadequate spinal anaesthesia required conversion to general anaesthesia (Table 7).

Table 7 *Analysis of group B excluding one outlier [UApH 7.09]. 7.32 (7.31–7 33), **P=0.011

	Group A	Group B
Umbilical artery pH, mean (95% CI)	7 32 (7.31–7.33)	7 31 (7 27–7 34)*
UD interval, median (IQR)	70 (52–110)	84 (48–114)
Phenylephrine dose (µg), median (range)	400 (100–1400)	100 (0–300)
Subjects given atropine (mg)**, *n*	13	6
SAP as percentage of baseline, mean (95% CI)	99.0 (95.4–102.6)	94 4 (91 3–97.5)
Subjects with hypotension (*n*), (SAP <70% of baseline)	3	2

We conclude that UApH at delivery is satisfactory when phenylephrine is used during spinal anaesthesia for elective Caesarean section. We have not shown a benefit to the fetus in giving phenylephrine when maternal SAP has decreased by only 5% from baseline.

Keywords: anaesthetic techniques, subarchnoid; sympathetic nervous system, phenylephrine

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A comparison of 0.0625% ropivacaine or bupivacaine combined with fentanyl 2 µg ml^{-1} administered by patient-controlled epidural analgesia in labour

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The relative potency of ropivacaine compared to bupivacaine when used for epidural analgesia in labour is controversial.[1] A double-blind randomized controlled comparison of the two drugs (concentration 0.0625%) combined with fentanyl 2 µg ml^{-1} was performed during the first stage of labour using patient controlled epidural analgesia (PCEA).

Sixty term primigravid women in early labour were enrolled. Analgesia was established using 15 ml of 0.125% ropivacaine or bupivacaine with fentanyl 5 µg ml^{-1} injected through a lumbar epidural catheter, with a further 5 ml given after 15 min if required. Thereafter, PCEA was used: local anaesthetic 0.0625%; fentanyl 2 µg ml^{-1}; 5 ml bolus; 10 min lockout; and no background infusion. Inadequate analgesia was treated with 10 ml of 0.1% trial drug without fentanyl. Hourly drug consumption, rescue dose requirement, sensory and motor block, VAS of pain during

Table 8 Comparison of bupivacaine and ropivacaine. Results are given as mean (SD) or number (%)

Patients (*n*)	Bupivacaine (*n*=25)	Ropivacaine (*n*=28)	95% CI for difference
Entry cervical dilatation (cm)	2 5 (0 8)	2.6 (1 0)	–0 67 to +0 3
Drug consumption (ml h^{-1})	14 2 (2 9)	15 4 (3.9)	–3 5 to 0 6
Rescue doses	14 (56%)	13 (46%)	17–36%
Median VAS h^{-1} (mm h^{-1}) (IQR)	16 [10–24]	16 [7–20]	*P* 0 43 Wilcoxon
Mode of delivery			
Vaginal	10	14	Fischer exact *P*=0 045
Forceps	11	4	
Caesarean	4	10	

contractions and incidence of side effects were recorded. Statistical analysis was with an unpaired *t*-test for differences between means or proportions and Fischer's exact test as appropriate.

Patient characteristics and duration of labour were similar in the two groups. No patient developed motor block. Side effects of nausea and pruritis were infrequent and of minimal severity (Table 8).

We were unable to reject the null hypothesis that there was no difference in rate of solution used per hour at a significance level of 0.05. Whilst PCEA with 0.0625% ropivacaine or bupivacaine combined with fentanyl provided effective analgesia, half the patients required at least one rescue dose.

Keywords: anaesthetic techniques, epidural; anaesthetics local, ropivacaine; anaesthetics local, bupivacaine

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The comparative obstetric mobile epidural trial (C.O.M.E.T.). A radomized controlled trial: pain relief

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Epidural analgesia is associated with increased rates of obstetric intervention.[1] Trials demonstrating adverse effects have examined traditional epidural techniques, which commonly result in dense motor block. Low dose 'mobile' techniques using solutions of opioid with low concentration local anaesthetic to preserve motor function are associated with increased maternal satisfaction[2] and reduce instrumental vaginal delivery rate.[3] We present a comparison of pain scores after traditional epidural analgesia for labour and two low dose techniques.

A total of 1054 primiparous women, requesting epidural analgesia, were randomized to receive intermittent boluses of 0.25% bupivacaine (traditional), combined spinal epidural (CSE) followed by intermittent boluses or low dose infusion (LDI), each using 0.1% bupivacaine with fentanyl 2 $\mu g\, ml^{-1}$. Visual analogue pain scores (VAS) were recorded before epidural insertion, at 5 min intervals for the first 30 min and hourly thereafter until delivery.

Compared with traditional epidural analgesia, CSE has a more rapid onset and its greater efficacy is maintained 1 h later (Table 9). However, at 3 h median VAS was significantly higher and no advantage was apparent at delivery. Throughout labour and at delivery there were no differences in VAS between traditional and LDI groups.

Table 9 VAS scores $^{**}P<0.001$, $^{*}P<0.01$ (Mann–Whitney *U* test)

Epidural technique	**Median VAS at time after epidural**					
	Pre-block	**5 min**	**20 min**	**1 h**	**3 h**	**Delivery**
Traditional (*n*=353)	75	64	12	14	15	25
CSE (*n*=351)	78	20**	0**	4**	21*	40
LDI (*n*=350)	75	57	18	10	12	23
n (Total)	1005	939	945	881	589	481

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Keywords: anaesthetic techniques, epidural; anaesthesia, obstetric

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Predictors of dissatisfaction with epidural analgesia during labour

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Maternal satisfaction with epidural analgesia during labour is an outcome commonly used for audit and research in obstetric anaesthetic practice. Despite being subjective and prone to influence by non-anaesthetic factors, maternal satisfaction remains the most practical way of assessing the efficacy of epidural analgesia from the woman's point of view. Many large obstetric units use fixed procedure epidural regimens for all their patients. If it were possible to predict which patients were more likely to be dissatisfied with a given regimen, an alternative technique could be targeted appropriately. We, therefore, set out to find predictors of both maternal and midwife dissatisfaction with the fixed procedure epidural and combined spinal epidural (CSE) regimens used in our unit.

The Wansbeck Epidural Audit System (Xentec, UK) was used to collect comprehensive patient characteristics, procedural, obstetric, and follow-up data from 5089 consecutive labour epidurals. All patients received epidural or CSE techniques using 0.1% bupivacaine with fentanyl 2 $\mu g\, ml^{-1}$. Microsoft Access 1997 was used to collate these data, defining epidurals with excellent scores from both patient and midwife as 'successful', and all others as 'poor'. These were compared using a Mann–Whitney *U* test and chi-squared test as appropriate. The predictive value of these factors was tested by backward stepwise logistic regression.

Satisfaction data were available from 4855 epidurals, of which 3633 (74.8%) were defined as successful and 1222 (25.2%) poor. Of the many variables considered, multiparity ($P<0.0001$), increasing body weight ($P<0.02$), the use of epidural rather than CSE ($P<0.0006$), and vaginal rather than operative delivery ($P<0.0001$) were associated with poor epidural satisfaction. The sensitivity of these predictors was not high.

The implication from these data is that we might improve our unit's results by targeting multiparous, obese women with a CSE technique. This approach is currently being tested. The bizarre finding of reduced satisfaction after vaginal deliveries may relate to the relatively poor performance of low dose epidurals during the second stage of labour. These findings are only relevant to the epidural techniques and patient mix found in our unit, so we cannot comment on the wider applicability of our clinical conclusions.

Keywords: analgesic techniques, epidural; analgesia, obstetric

Investigation into the use of a new oesophageal pulse oximeter in cardiothoracic surgery patients

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Conventional pulse oximetry may fail when peripheral circulation is compromised.[1 2] We have investigated the use of a new oesophageal reflectance pulse oximeter[3] in a group of patients with poor peripheral perfusion based on the hypothesis that blood flow to this central site may be preferentially preserved.

After induction of anaesthesia in 50 elective cardiothoracic surgery patients a purpose-built oesophageal reflectance pulse oximetry probe was positioned in the oesophagus. Signals were recorded at various depths of the oesophagus, as the probe was withdrawn, until the site of best signal was determined. Monitoring in theatre was intermittent and during these periods the saturation readings were compared with the arterial saturation of blood gases and co-oximetry results.

Signals were recordable in all 50 patients and oxygen saturation readings were in good agreement with arterial blood gas and co-oximetry results. The results were compared using Bland Altman analysis (Fig. 1). Five of the patients showed a period of peripheral pulse oximetry failure while oesophageal signals remained. These failures occurred on the intensive care unit, when patients were peripherally cool.

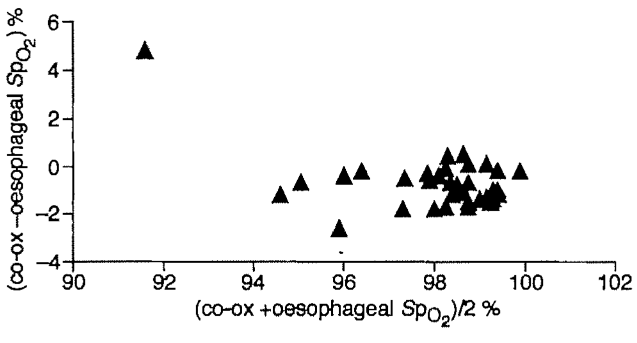

Fig 1 Difference against mean for oxygen saturation data from oesophagus and co-oximetry.

Peripheral pulse oximetry signals are often difficult to obtain in patients with poor peripheral perfusion. Oesophageal pulse oximetry may be a useful alternative way of monitoring arterial oxygen saturation in such patients.

Keywords: gastrointestinal tract, oesophagus; measurement techniques, pulse oximetry

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Continuous arteriovenous oximetry as a measure of perfusion during hypothermic cardiopulmonary bypass

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Whilst considerable research is directed at the causes of neurological injury during bypass,[1] the significance of sudden bypass flow reductions on oxygenation may have been overlooked. It is assumed that cooling protects from ischaemia when bypass flow is reduced to aid surgery. The duration of safe flow reduction has not been determined.[2] Previous studies have attempted to analyse oxygenation from blood sampling.[1] This is not rapid enough to study sudden changes. Continuous arteriovenous oximetry provides a ready method of studying oxygenation during acute flow alterations.

Elective coronary surgery patients received standardized etomidate, alfentanil, rocuronium, and isoflurane anaesthesia. Routine bypass flows of 2.4 litres m^{-2} min^{-1} were used with fresh gas flows adjusted to maintain a Pa_{O_2} of 25–30 kPa and Pa_{CO_2} of 4.5–5.5 kPa. Isoflurane (1%) was administered in the fresh gas. Arterial and venous saturations from oximeters (Ghish Biomedical) on respective bypass circuit limbs were collected by a Labview chart recorder. Simultaneous recordings of pump flow rate were down loaded. Oxygen consumption and delivery were calculated every 3 s. During flow down, oxygen deficit was calculated by subtracting the oxygen actually consumed from the amount that would have been consumed in the same time interval at full flow rate. After flow restoration, the 'recovery' amount of oxygen consumed above basal was calculated similarly (Fig. 2).

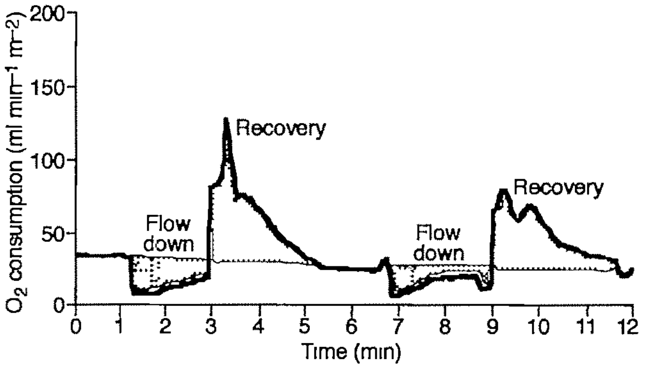

Fig 2 Baseline, flow down, and recovery oxygen consumption Recovery oxygen consumed is 2.3 times greater than the flow down deficit

Six patients, (five male and one female) (results; mean (SD) age 60.2 (13.2), surface area 1.81 (0.14) m^2, underwent a bypass of 103 (18) min at a temperature of 31.3 (0.94)°C. Eight flow down events longer than 1 min were analysed. Calculated flow down oxygen deficit, correlated significantly with oxygen consumed during recovery r=0.719 (P=0.022).

Information from arteriovenous oximetry may be used to calculate safe flow down intervals, and optimize bypass flow rates taking account of individual patient's metabolic demands.

Keywords: measurement techniques, oximetry, arteriovenous; surgery, cardiovascular, cardiopulmonary bypass

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The effect of methylprednisolone on uninary N-acetyl-β-D-glucosaminidase/creatinine ratios in porcine vascular surgery

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Urinary *N*-acetyl-β-D-glucosaminidase/creatinine ratio (NAG/creatinine) has been shown to be a sensitive indicator of subclinical proximal tubular damage, and at higher levels correlates with raised plasma urea and creatinine.[1] The perioperative inflammatory response may contribute to renal injury.[2] Methylprednisolone reduces elements of the inflammatory response perioperatively.[3] We hypothesize that in a porcine hind limb ischaemia-reperfusion model prior administration of methylprednisolone may reduce perioperative renal injury.

Twelve 10–12-week-old male pigs were anaesthetized (40 mg kg^{-1} induction then 13 mg kg^{-1} h^{-1} maintenance) and immediately underwent laparotomy, normodynamic fluid resuscitation for 2 h followed by bilateral hind-limb ischaemia for 2 h followed by 2.5 h of reperfusion. Pigs were randomied to two groups. Group C received placebo and group MP received methylprednisolone 30 mg kg^{-1} at induction of anaesthesia. Urine samples were obtained as follows: 30 min after anaesthesia induction (baseline sample **a**), 2, 3, 4, 5, and 6.5 h post-induction (samples **b**, **c**, **d**, **e**, and **f**). Urinary NAG/creatinine was measured at each sample time. Analysis between groups was with the Mann–Whitney *U* test and within groups with Wilcoxon matched pairs.

At samples **d** and **e** (end of ischaemia and 1 h into reperfusion) NAG/creatinine was significantly lower in the MP group (Fig. 3).

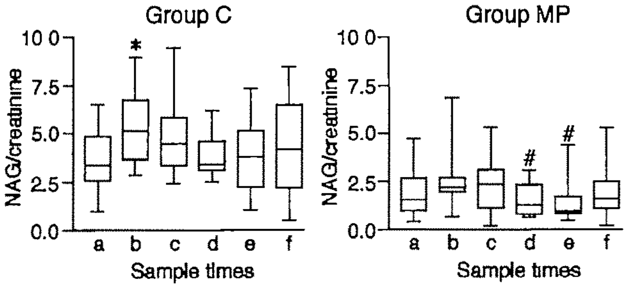

Fig 3 NAG/creatinine ratios in Group C (*n*=6) and group MP (*n*=6). Box and whisker plots show median, 25th and 75th percentiles and range. *$P<0.05$ within group compared with baseline. #$P<0.05$ between groups.

This porcine model may therefore be a useful tool to elucidate mechanisms of perioperative renal injury at vascular surgery and possible protective mechanisms of methylprednisolone.

Acknowledgements: This research is supported by the British Heart Foundation.

Keywords: surgery, vascular; complications, renal damage

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Subclinical perioperative myocardial injury in patients undergoing major vascular surgery

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The risks of cardiac morbidity and mortality associated with major vascular surgery are well known. We describe a prospective cohort study of perioperative myocardial injury in patients who either had cardiac disease or had risk factors for cardiac disease and who underwent elective major vascular surgery in five participating hospitals.

Clinical, ECG, and laboratory data were collected from subjects before surgery. Subjects were followed up until hospital discharge or death. Blood samples for cardiac troponin I (cTnI), and a 12-lead ECG were obtained preoperatively and on each of the first four postoperative days. Blood samples were centrifuged, frozen, and stored locally before being transferred to the University of Bristol for analysis, using the ACCESS™ immunoassay system. The cTnI cut-off for the diagnosis of myocardial infarction using this assay is 0.15 µg $litre^{-1}$.[1] All ECGs were reviewed by a Reader in Cardiology (AB) and new changes recorded.

Sixty-three patients were studied, mean age 70.4 (SD 9.4, range 00–00) yr. Fifty-two (88%) were male. Fifteen patients (25%) displayed cTnI elevations consistent with a myocardial infarction (>0.15 µg $litre^{-1}$). Post hoc analysis suggested that these patients could be divided into two distinct groups. Eight patients had transient and relatively modest cTnI elevations. In this group the median peak cTnI level was 0.20 µg ml^{-1} (range 0.16–0.56) One of these patients developed atrial fibrillation in the postoperative period. This was accompanied by ST-segment depression on the ECG and clinical evidence of heart failure. One other patient developed heart failure without associated ECG changes. The remaining six patients had no clinical evidence of a perioperative cardiac complication. Seven patients suffered more protracted bouts of cTnI release associated with higher peak cTnI levels, median 2.41 µg $litre^{-1}$ (range 0.68–14.42). All seven of these patients suffered an ischaemic cardiac event diagnosed clinically or from the ECG.

These data show that significant cTnI release occurs in the absence of clinical evidence of acute myocardial injury in some patients undergoing major vascular surgery. The findings are consistent with work showing transient cTnI release in patients undergoing cardiac surgery.[2]

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Keywords: surgery, vascular; complications, myocardial injury

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Risk factor stratification for adverse outcome in vascular surgical patients

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We have examined the association between clinical risk factors, perioperative silent myocardial ischaemia (SMI) and elevated serum cardiac protein concentrations (troponins I and T, TnI and TnT, and CK-MB) as markers of cardiac outcomes in patients undergoing vascular surgery.

Patients (aged 42–97 yr, *n*=208, 160 male) undergoing vascular surgery were recruited. The presence of 12 clinical risk factors was determined by history and clinical examination. Perioperative Holter monitoring was conducted in 191 patients and blood sampling for cardiac proteins in 105 patients. Patients were followed-up for 1 yr. Three models were generated by logistic regression (SPSS, v9.0) for both early (≤1 month) and overall outcomes (up to 1 yr) using: clinical risk factors (Model 1); SMI and clinical risk factors (Model 2); SMI and clinical risk factors plus increase in serum cardiac protein levels (Model 3).

There were 40 adverse outcomes—31 in the first month and nine more in the 12 months after surgery. In Model 1, logistic regression analysis identified histories of angina, congestive cardiac failure (CCF), or smoking as predictors of early outcome and histories of angina or CCF as predictors of overall outcome. For Model 2, the predictors of early adverse outcome were: angina, smoking, SMI, and CCF; only angina and SMI remained predictors of overall adverse outcome. In Model 3, CK-MB, SMI, and angina were all predictors of early and overall outcome (see Table 10).

We conclude a history of angina to be the most important clinical risk factor for predicting adverse outcome in our population, but SMI, a history of CCF and smoking are also useful markers. Our results are similar to those of Pasternack and colleagues and Fleisher and co-workers[1 2] for vascular populations; but we did not find troponins to be useful indicators of outcome. This may reflect the small numbers of patients with elevated troponins and adverse outcomes in this group.

Acknowledgments: This study was supported by the Wellcome Trust from 1992–1997 and by LMA International from 1999 to date.

Keywords: surgery, vascular; risk

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Thrombelastograph® and laboratory markers of thrombophilia

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Using Thrombelastograph (TEG®) coagulation analyser, we have demonstrated that men, women and pregnant women represent a trend of increasing coagulation.[1] Hypercoagulability during pregnancy has been attributed to increased concentrations of fibrinogen, factors V, VII, VIII, X, XI, and decreased concentrations of proteins C and S[2]. TEG® has been described as a device capable of identifying thrombotic tendencies,[3] but has never been shown to correlate with conventional laboratory markers of thrombophilia. Pregnant women offer a natural reservoir of physiological thrombophilia. The aim of this study was to correlate TEG® and conventional laboratory markers of thrombo-

Table 10 *P* values of risk factors for adverse cardiac outcome. (NS, not significant)

Risk factor	Model 1 Early	Overall	Model 2 Early	Overall	Model 3 Early	Overall
Angina	0.002	0.003	0.004	0.007	0.035	0.091
CCF	0.006	0.056	0.018	NS	NS	NS
Smoking	0.009	NS	0.006	NS	NS	NS
SMI	–	–	0.016	0.006	0.074	0.013
CK-MB	–	–	–	–	0.001	0.005

Table 11 Correlation values *Significant at *P*<0.05, **significant at *P*<0.01

TEG®	PT APCR	APTT Prot C	Fib Prot S	V AT III	VII	VIII	X
r	NS	NS	–0.21**	NS	–0.22**	–0.26**	–
0.29**	0.26**	NS	0.21*	NS			
k	NS	NS	–0.42**	NS	–0.35**	–0.37**	–
0.37**	0.36**	NS	0.37**	NS			
α	–0.17*	NS	0.51**	NS	0.36**	0.36**	
	0.32**	–0.33**	NS	–0.38**	–0.17**		
MA	–0.21*	NS	0.70**	NS	0.42**	0.44**	
	0.44*	–0.45*	0.19#	–0.45*	NS		

philia using subjects demonstrating the range of naturally occurring thrombotic tendency.

We recruited 150 ASA I volunteers; 50 pregnant women at term, 50 men and 50 non-pregnant women. Anyone with a history of thromboembolism, or taking anti-platelet drugs was excluded. A 22G cannula was inserted into a forearm vein. After discarding the first 2 ml to avoid contamination by tissue thromboplastin, 10 ml of blood was taken for TEG® analysis and for a modified thrombophilia screen, including PT, aPTT, fibrinogen, factors V, VII, VIII, X, activated protein C resistance (APCR), proteins C and S, and antithrombin III (AT III). TEG® was performed on fresh whole blood using disposable cups and pins in a standardized manner. Statistical analysis was performed using Pearson's correlation *r*.

Results of significant correlation (*r*) are shown in Table 11.

TEG® analysis correlates strongly with fibrinogen, factors VII, VIII, and X, APCR and protein S. Weak correlations were found with prothrombin time, protein C and AT III TEG® analysis may have potential for use as a simple, inexpensive, rapid, point of care screening tool for thrombophilia in high risk patients, and this needs further investigation. Results of TEG® analysis may be used to determine which patients require further investigation or treatment.

Acknowledgements: Source of Funding: Obstetric Anaesthetists Association and Yorkshire Regional Health Authority

Keywords: equipment, Thrombelastograph®; blood, thrombocytopenia

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When is it safe to site an epidural in patients on high dose enoxaparin?

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High thoracic epidural analgesia in patients undergoing coronary artery bypass has been associated with reduction in the stress response,[1 2] better analgesia,[3] earlier extubation,[4] and fewer serious arrhythmias.[4] These benefits are particularly attractive in patients with unstable angina undergoing surgery. However, patients with unstable angina are now treated with enoxaparin 1 mg kg^{-1}. It has been recommended that patients on low molecular weight heparin (LMWH) should not have an epidural until 10–12 h after receiving up to 40 mg enoxaparin.[5] We have used Thrombelastograph® coagulation analysis and factor Xa inhibition to investigate how long it takes for coagulation to return to control levels after high dose enoxaparin.

Forty patients were studied. Twenty patients were control undergoing elective coronary artery bypass surgery and 20 were receiving enoxaparin 1 mg kg^{-1} daily. The control patients had a 5 ml blood sample taken before induction of anaesthesia and the enoxaparin group had 5 ml blood samples taken at 6, 8, 10, 12, and 24 h after subcutaneous enoxaparin 1 mg kg^{-1}. Each sample underwent Thrombelastograph® coagulation analysis immediately and was analysed for factor Xa inhibition subsequently.

There were no significant differences between the groups in height, weight, age, sex, or smoking history ANOVA and Student's *t*-test demonstrated a significant increase at the 5% level in factor Xa inhibition and prolongation of the *r* value but not maximum amplitude on Thrombelastograph® analysis at 6, 8, 10, and 12 h. At 24 h the *r* value and factor Xa inhibition had returned to control levels (Table 12). There was a statistically significant correlation between *r* time prolongation and factor Xa inhibition with an r^2 value of 0.67.

Table 12 Values are expressed as means with standard deviation (SD) *Signifies a significant result at the 5% level

	MA (mm)	**Xa Inhibition (iu ml^{-1})**	***r* value (mm)**
Control	61 4 (6 4)	0 05 (0 05)	20 (0 27)
6 h	55 7 (8 2)	0.67 (0 07)*	40 (7 5)*
8 h	57 (7 1)	0 6 (0 1)*	34 (7 5)*
10 h	58 2 (6 1)	0 42 (0 08)*	31 (6.25)*
12 h	60.0 (7 5)	0 28 (0 075)*	27 (5)*
24 h	60 7 (7 3)	0.04 (0 03)	20 5 (0 33)

We conclude that it is necessary to wait 24 h after high dose enoxaparin before siting an epidural. Our results also suggest that the *r* value may be a useful surrogate for factor Xa inhibition in patients on enoxaparin.

Keywords. anaesthetic techniques, epidural; blood, coagulation, enoxaparin

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Effect of transcervical papaverine and bupivacaine on postoperative analgesia after laparoscopic application of filshie clips

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In comparison with diagnostic laparoscopy, Filshie clips applied during laparoscopic sterilization can cause additional abdominal pain induced by ischaemia or spasm. Papaverine is a smooth neuromuscular blocking agent that may improve this pain if administered directly to the fallopian tubes. Previous trials evaluating administration of transcervical bupivacaine[1] and lignocaine[2] to Filshie clips have shown positive results. The aim of the study was to evaluate if transcervical papaverine would reduce this pain and to compare this effect with those of bupivacaine and placebo.

Sixty-six ASA I–II females, undergoing laparoscopic sterilization, were recruited and allocated randomly to either papaverine 30 mg or 0.375% bupivacaine 30 ml or 30 ml of saline. Patients were given a standard anaesthetic comprising propofol 2–4 mg kg^{-1}, fentanyl 1 mg kg^{-1} and a neuromuscular blocking agent. Patients' lungs were ventilated to normocapnia with nitrous oxide and isoflurane in oxygen via a standard laryngeal mask airway.† Suppositories of diclofenac 100 mg and i v ondansetron 4 mg were given Before application of a Filshie clip to the medial third of each Fallopian tube, the appropriate solution was injected through a Spackman's cannula placed into the cervix of the uterus. Residual neuromuscular block was antagonized with neostigmine 2 5 mg and glycopyrrolate 500 mg at the end of surgery.

Postoperatively, rescue analgesia comprised two tablets of cocodamol 30/500 and i.m. morphine 10 mg. Patients were assessed as soon as they were awake (time 0), at 30 min and then at 1, 2, 3, and 4 h by an observer blinded to the treatment. Exclusion criteria were allergies to bupivacaine and papaverine, chronic pain syndrome, pelvic inflammatory disease and adhesions, regular analgesic ingestion and operative difficulties.

Of 66 patients recruited, three did not complete the study. There were no significant differences between the three groups in age and median body mass index. Analgesic consumption did not differ significantly between the groups in terms of. number of patients having analgesia within the first postoperative hour; number of patients having cocodamol only, morphine only or the combination of cocodamol and morphine. There were no significant differences between median visual analogue pain scores, sedation scores, incidence of postoperative nausea and vomiting, and requirement for rescue antiemetics. In conclusion, transcervical papaverine did not provide additional analgesia for laparoscopic sterilization.

Keywords: surgery, laparoscopic sterilization; analgesia, postoperative

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Efficacy of transcutaneous spinal electroanalgesia on thermal sensation and pain thresholds in healthy volunteers

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Recently modified TENS machines, which are capable of delivering extremely brief (4 ms) electrical pulses are now available.[1] The pulses are thought to penetrate deep enough to exert modulating effects within the spinal cord. This technique is called Transcutaneous Spinal Electroanalgesia (TSE). It has been shown to improve general mood and pain tolerance in healthy normal subjects.[2] Quantitative Sensory Testing (QST) allows physiological measurement of sensory neurological function, including tolerance to hot and cold stimuli.

Twenty healthy individuals were recruited in this randomized double-blind crossover trial. After a normal neurological examination, QST was performed on the thenar eminence of the dominant hand before and after TSE treatment. A psychological questionnaire of positive and negative mood states (Positive and Negative Affect Schedule) was also performed before and after treatment. Each volunteer repeated the session twice on two separate days receiving either active or control TSE treatment. Power analysis revealed that based on Towell, Williams and Boyd's work, 16 individuals would be needed to detect a 20% change of threshold in temperature (°C). Statistical analysis was carried out using a paired *t*-test for quantitative data.

There were no significant differences between active and control treatments in any of the measured variables (Table 13).

We have found that a single treatment of TSE does not significantly affect thermal sensation, pain sensation, or mood in healthy volunteers.

Keywords: pain, heat sensation; pain, threshold

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The effect of obturator nerve block on chronic hip pain

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Osteoarthrits of the hip is a common condition, which leads to pain and disability. It has been demonstrated that regional block of the hip can lead to increased range of movement in patients who have limited mobility.[1] Patients who have osteoarthritis of the hip attend the pain clinic while waiting for arthroplasty, presenting with pain, limited movement and poor quality of life. The aim of our study was to assess in the outpatients setting the effect of obturator nerve block on hip function and depressive symptoms in ambulant patients with osteoarthritis of the hip.

Ten adult patients who attended the outpatients' clinic with osteoarthritis of the hip were studied. A full history and examination was performed. A physiotherapist assessed pain, functional ability, and activities from which a Harris hip score was calculated. A full range of movement was measured. The co-existing psychological symptoms were assessed by applying the Zung scoring system. A pain intensity score was obtained (range 0–10). A separate investigator performed an obturator nerve block. This was performed by an anterior approach with full aseptic technique and the use of a peripheral nerve stimulator to localize the nerve. A constant current of less than 1 mA was used. Five to seven millilitres of 0.5% bupivacaine was used. The patient was rested in the supine position. After 30 min the range of movement was measured by the same physiotherapist.

The patients were reassessed after 6 weeks and 3 months. At this stage a full history and examination was performed. A movement score, Harris hip score, Zung score, and pain intensity score were measured. Wilcoxon signed rank test was used to analyse the data.

We demonstrated an immediate improvement in movement score after the procedure, which persisted for 6 weeks. Median movement scores were 82 initially which then increased to 96 immediately after block (P=0.005) and then 98 after 6 weeks (P=0.03). After 12 weeks movement returned to the baseline state. Obturator nerve block significantly decreased pain intensity score

Table 13 Comparison of active and control TSE treatments

Variable	Change °C active TSE (mean (SD))	Change °C control TSE (mean (SD))	Significance P value and (95% CIs)
Cold sensation	0.05 (0.7103)	0 1212 (0.81)	0 779 (–0.4,0.5)
Warm sensation	–0 01 (1.22)	0.2750 (0.7651)	0 403 (–0 41, 0 93)
Cold pain	–1 22 (3.1)	–0.6 (3 7)	0 502 (–1.03,2.4)
Heat pain	–0 1180 (1 7)	0.61 (3 06)	0 829 (–1 5,1 8)
Positive affect	0.9 (2.3)	0.1 (2 26)	0.371 (–2 6,1)
Negativea affect	0 25 (1 2)	0.15 (1 2)	0.776 (–0 8,0 6)

after 6 weeks ($P=0.03$) but after 12 weeks pain intensity scores returned to baseline levels. Median Zung scoring decreased from 25 to 19 after 6 weeks ($P=0.09$) then 18 after 12 weeks ($P=0.18$). We did not demonstrate a significant change in Harris hip score over the period of the study.

We conclude that obturator nerve block causes an immediate improvement in range of movement in patients who have osteoarthritis of the hip. The increase in movement persists for 6 weeks. This increase in movement is associated with a decrease in pain intensity score over the same period of time. We report that this may be a clinically valuable outpatient technique to improve symptoms in patients awaiting surgery.

Keywords: pain, chronic; anaesthetic techniques, regional, obturator nerve block

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Spread of injectate with superficial cervical plexus block in the cadaver

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Carotid endarterectomies are commonly performed using either a superficial cervical plexus block or a combined (superficial and deep) block.[1] The deep block is designed to deposit local anaesthetic close to nerve roots and might be expected to provide better anaesthesia and muscle relaxation However, both blocks are equally effective.[1] The anatomy of the superficial cervical space might explain this finding. Winnie and colleagues described the spread of injectate during deep block,[2] but the spread during superficial block has not been examined.

We used six cadavers. Injections were made using a 23G needle and 30 ml syringe. In two cadavers (C1, C2), we performed an injection of 30 ml 0.01% methylene blue dye into the intact neck, just deep to the investing fascia, as if performing a superficial cervical plexus block In two cadavers (C3, C4), we first dissected away skin to expose the investing fascia. We then injected dye just deep to this fascia. We performed two 'control' injections. In cadaver C5, dye was injected only subcutaneously. In cadaver C6, we performed a standard deep cervical plexus block. In all cadavers we performed careful dissection to ascertain the spread of dye.

In C1 to C4, dye was found in the superficial space just below the investing fascia and also deep to the prevertebral fascia, coating the scalene muscles and the phrenic nerve. In C1 and C3, dye was even found to be tracking down to the axillary sheath, suggesting communication between the superficial cervical space and the brachial plexus. In C5, dye remained subcutaneous and did not spread. In C6, the dye was confined to the deep cervical space, with no retrograde spread to the superficial space.

We have demonstrated the potential for communication between superficial and deep spaces of the neck. Traditionally, the prevertebral fascia is regarded as impenetrable, at least by infections and tumours.[3, 4] Our novel result might, however, explain the observation that both deep and superficial blocks have equal efficacy: the local anaesthetic enters the same anatomical spaces. We might speculate that a large volume of injectate might open up channels in the prevertebral fascia, whereas these channels might be closed by inflammatory processes Microscopic tumour spread along the perineurium from superficial to the deep roots of the cervical nerves has been demonstrated, suggesting that routes may exist between the two spaces of the neck.[5] Artefacts produced by cadaver fixation are unlikely in view of our control results We conclude that in the normal human neck, the superficial and deep spaces communicate and that this might underlie the observed efficacy of superficial block for carotid artery surgery.

Keywords: anaesthetic techniques, cervical plexus block; anatomy

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Evaluation of early extubation after liver transplantation

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The safety and efficacy of early extubation after liver transplantation are controversial. A recent study suggested that 18% of patients were suitable for this procedure[1] and had similar outcomes (including reintubation rates) to patients ventilated postoperatively. We have recently implemented a fast-track procedure using broad entry criteria, and collected data to assess the safety and wider applicability of the technique.

Over a 1-yr period we performed 120 liver transplants. Of these, we considered 78 elective liver transplant patients as potentially suitable for fast tracking, defined as in-theatre extubation and early discharge to the ward. Patients with fulminant liver failure, those who were inotrope or dialysis dependent, and those with significant cardiac disease were excluded. Patients were anaesthetized using a modified anaesthetic technique using short acting agents, including remifentanil[2] and desflurane [3] In those whose platelet count exceeded 80×10^{9} litre^{-1}, a thoracic epidural catheter was placed for postoperative analgesia The remainder received PCAS morphine postoperatively. Patients were managed according to a standard procedure.[4] Extubation was attempted in theatre wherever the anaesthetist felt this possible. ITU stay, hospital stay, reintubation rate, and graft function were studied We also studied preoperative factors indicative of successful extubation.

Of the 78 patients enrolled, 59 (78%) were successfully extubated. Forty patients received epidurals, of whom 34 were extubated. Twenty-five of 38 patients allocated to PCAS were extubated in theatre None required reintubation Preoperative creatinine (80 (3) *vs* 89 (6)), age (47, 41–54 *vs* 50, 37–59 yr), ALT, bilirubin, Child-Pugh score (7, 5–9 interquartile range in the extubated patients, *vs* 8, 4.5–10.5) and albumin (33 (0 8) vs 30 (1 4) g litre^{-1}) were similar between extubated and ventilated patients. PT was slightly lower in extubated patients, 15.6 (0.5) s *vs* 19 2 (2.3) s, $P<0.02$.

Postoperatively, fast-track patients had a shorter time to hospital discharge, 13 (11–18) days *vs* 25 (17–35) days, $P<0.0003$; and a shorter time in intensive care, 21 (3) h *vs* 5 (3.4) days, $P<0.0003$. Renal function was better postoperatively in the extubated group, creatinine 98 (10) *vs* 143 (19), $P<0\ 05$. After construction of a propensity score for early extubation ($P=0\ 004$), a quintiles analysis suggested that patients suitable for fast tracking would have a hospital stay shorter by 17 days than those not, but that a 15 day reduction in stay could be attributable to the fast tracking process.

A majority of patients undergoing elective liver transplantation can be fast-tracked. Those sicker preoperatively are less likely to be successfully extubated in theatre. A randomized trial is required to establish whether reduced duration of stay is directly attributable to early extubation. Based on these data, such a study would need at least 26 evaluable patients per group for a power of 80% at the P=0.05 level

Keywords: anaesthesia; liver, transplantation

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Interleukin 13 and inflammatory markers in human sepsis

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Interleukin-13 (IL-13) is an anti-inflammatory cytokine whose effects include inhibition of the production of inflammatory cytokines, including TNF-α, IL-1β, IL-6, IL-8 by LPS-stimulated monocytes, prolongs survival of human monocytes and increases surface expression of MHC class II molecules and CD23. It strongly inhibits tissue factor expression induced by LPS and protects endothelial and monocyte surfaces. It has been shown in mice to protect against sepsis and is necessary for survival after CLP in mice.[1] To date, there are few reports of IL-13 in septic humans Therefore, we have assayed this cytokine, together with other markers of inflammation in human sepsis, to characterize its pattern of expression.

Thirty-one patients with sepsis or septic shock were recruited. Blood samples were taken from each patient on admission, days 1, 3, 5, and 7. Routine blood results were noted as well as descriptive data. A clotted sample was centrifuged at 2000 r.p.m. for 20 min and the serum frozen to allow later analysis. A high-sensitivity ELISA was used to quantify TNF-α. IL-13 and IL-2 were assayed by standard ELISA, and HLA-DR on CD-14 positive monocytes measured by flow cytometry after labelling with immunofluorescent monoclonal antibodies.

Patients had a median age 56 (45–69, interquartile range). APACHE II score was 17.5 (15–23). There were 24 men and seven women. Twenty-three of the 31 patients developed septic shock. Patterns of expression of HLA-DR were characteristic of previous reports of similar patient populations, showing greater depression and slower recovery in the shocked than the non-shocked patients (Fig. 4). IL-13 was detected in the plasma of 24 of the 31 patients at baseline.

TNF was elevated in all patients but more so in those with septic shock.

We have characterized patterns of IL-13 expression in human sepsis and septic shock. IL-13 may also pressage the recovery in HLA-DR expression on CD14 positive monocytes

Keywords: infection, sepsis; immune response, interleukin-13

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Biochemical predictors of outcome from intensive care

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An improved understanding of predictors in the intensive care unit (ICU) setting would provide prognostic information useful for making treatment decisions. The acute physiology and chronic health evaluation II (APACHE II) system is a widely used score to provide indications of probable outcome from intensive care. However, this system is largely based on physiological variables that may reflect propensity for change in response to the illness within the individual rather than disease severity itself. We, therefore, conducted a cohort observational study to assess the relationship between biochemical variables and mortality of ICU patients regardless of diagnosis.

Two hundred patients were recruited and a single blood sample taken within the first 24 h of ICU admission. Concentrations of plasma interleukin-6 (IL-6), lipid peroxide, and protein-bound thiol groups, plus total antioxidant capacity, were determined. Albumin, urate, lactate, prothrombin time, and fibrinogen were also recorded from the results of routine pathology laboratory measurements. Non-parametric data were expressed as median (range) and analysed by Mann–Whitney U test and normally

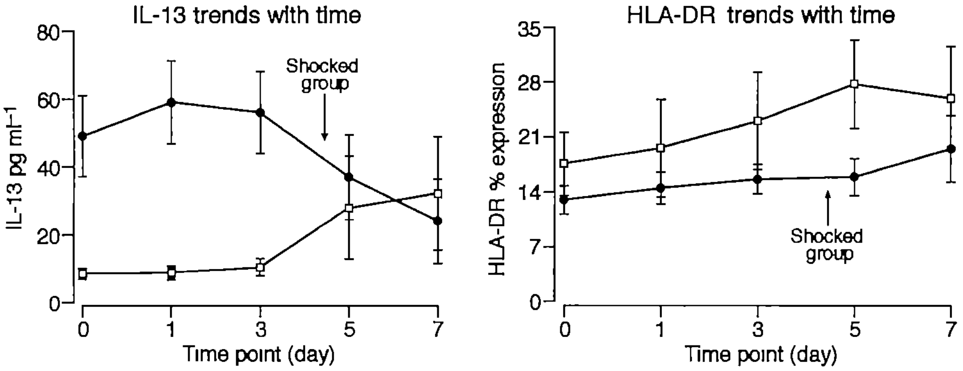

Fig 4 Patterns of expression of IL-13 and HLA-DR in shocked and non-shocked patients (mean (SEM))

distributed data were expressed as mean (SD) and analysed by Student's *t*-test.

Of the 200 patients recruited 114 were men and 86 were women, with a median age of 60 (18–92) yr. Median ICU stay was 3 (1–55) days; 45 patients died and 155 survived. Serum urate, lactate, and IL-6 were significantly higher in non-survivors than survivors 0.44 (0.12–0.93) *vs* 0.32 (0.10–1.04) mmol $litre^{-1}$; 2.9 (0.6–28.0) *vs* 1.8 (0.6–19.0) mmol $litre^{-1}$; 1547 (18–7682) *vs* 116 (10–4431) pg ml^{-1}, respectively ($P<0.001$ in each case). Antioxidant capacity was significantly lower in non-survivors (1.11 (0.16) mmol $litre^{-1}$) than survivors (1.26 (0.17) mmol $litre^{-1}$, $P<0.001$). Serum albumin and lipid peroxide concentrations were also significantly lower in the non-survivors 28.0 (8.2) *vs* 30.5 (6.6) g dl^{-1} and 2.20 (0.01–8.60) *vs* 3.13 (0.01–8.75) µmol $litre^{-1}$, respectively ($P<0.05$). Prothrombin time, fibrinogen concentrations and protein thiol group concentrations did not differ significantly between survivors and non-survivors. Logistic regression analysis revealed that IL-6, total antioxidant capacity and serum urate are independent predictors for ICU mortality (Table 14).

Table 14 IL-6, antioxidant and urate concentrations

Variable	*P* value	Odds ratio (95% confidence interval)
Interleukin-6 (pg ml^{-1})	<0.001	1.0009 (1.0005–1.0013)
Total antioxidant capacity (mmol $litre^{-1}$)	<0.001	0.0020 (0.0001–0.0350)
Urate (mmol $litre^{-1}$)	<0.05	18.853 (1.73–204.9)

The predicted ICU mortality can be estimated using the following equation:

$$\text{Logit }(P) = (\text{IL-6}\times 0.0009) + (\text{antioxidant capacity}\times -6.2253) + (\text{urate}\times 2.9367) + 4.1294$$

Acknowledgements: We gratefully acknowledge the help and cooperation of the ICU nursing and medical staff.

Keywords: intensive care

The effect of propofol and ketamine on phosphodiesterase activity

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The neurotransmitter activity of nitric oxide is involved in excitatory amino acid-mediated neurotoxicity, consciousness, learning, and memory. Effects on the nitric oxide–cGMP pathway have been implicated in anaesthesia. Most of the effects of nitric oxide are mediated by activation of guanylate cyclase leading to production of cGMP[1]. Sedative drugs decrease intracellular cGMP in the brain. This could be either a result of a decrease in production via effects on guanylate cyclase activity or increases in degradation of cGMP through increased phosphodiesterase activity. Several isoforms of phosphodiesterases metabolize the cyclic nucleotides cAMP and cGMP into the inactive compounds 5'AMP and 5'GMP, respectively. The aim of this study was to investigate the effects of anaesthetic agents on phosphodiesterase activity.

We adapted a spectrophotometric assay for measuring phosphodiesterase activity *in vitro*. The technique uses the change in absorbance at 340 nm in a series of coupled enzyme reactions using cAMP as substrate, in the presence of NADH. Analyses were conducted in triplicate at four concentrations of propofol and ketamine, at enzyme substrate concentrations ranging from 0.5 to 10 K_m. Lineweaver–Burke plots were then constructed in order to determine the effects of propofol (10, 1, 0.1, and 0.01 µM) and ketamine (100, 10, 1, and 0.1 µM) on K_m and V_{max} of a mixture of phosphodiesterases purified from bovine heart. Results were expressed as percentage change compared with K_m and V_{max} in the absence of the anaesthetic agent. Single linear regression analysis was used and $P<0.05$ was considered statistically significant.

Neither propofol nor ketamine changed V_{max}. Propofol reduced K_m by 58.9 and 79.6% at 10 and 1 µM, respectively ($P<0.01$) whereas lower concentrations had no effect. Ketamine had no effect on K_m at any concentration. Neither of the anaesthestics had any affect on the activity of any of the other coupled enzymes used to determine phosphodiesterase activity.

A reduction in K_m in the absence of a change in V_{max} is indicative of an enzyme agonist, whereas an increase in K_m is suggestive of a competitive antagonist. We have shown that at concentrations relevant to those obtained in the circulation clinically, propofol acts as an agonist in this *in vitro* setting. Further investigations are required to determine which particular isoforms of the phosphodiesterases are affected by these anaesthetic agents.

Acknowledgements: We are grateful to the Royal College of Anaesthetists and the Association of Anaesthetists for financial support.

Keywords: enzymes, phosphodiesterases; anaesthetics i.v., propofol; anaesthetics i.v., ketamine

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Propofol and halothane vs sevoflurane in paediatric day case surgery: induction characteristics and recovery time

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As day case surgery aims to minimize disruption of the patient's routine, anaesthetic agents that enable a safe and rapid return to the community should be used.[1] The aim of this study was to compare the induction characteristics and recovery time of a propofol induction and maintenance with halothane/N_2O/O_2, or sevoflurane/N_2O/O_2 induction and maintenance in paediatric patients.

Three hundred and twenty two unpremedicated children, aged 3–13 yr undergoing day case general or ENT surgery were randomized to receive either a propofol (with lidocaine) induction with halothane/N_2O maintenance, or a sevoflurane/N_2O induction and maintenance technique. Time from starting anaesthesia until entering the operating theatre (induction time), anaesthetic maintenance time, and times when ready to leave the recovery room and go home were noted. The incidence of adverse events during induction was recorded. Statistical analysis using $SPSS^{TM}$10 was carried out with unpaired Student's *t* or chi-squared tests as appropriate (Table 15).

The children who had propofol had a shorter induction time than those having an inhalation induction with sevoflurane. In contrast, the children who had anaesthesia maintained with sevoflurane had a shorter recovery time than those in the

Table 15 Comparison of propofol/halothane and sevoflurane groups. Mean (SD) where appropriate

Group (*n*, number per group)	Propofol/halothane (*n*=156)	Sevoflurane/sSevoflurane (*n*=166)	*P*
Age (yr)	7.2 (2.6)	7.17 (2 7)	n s
Female.Male	1 2 1	1 2 3	n.s.
Induction time (min)	3 1 (1 9)	5 0 (2 3)	0.001
Maintenance time (min)	9.5 (7 0)	10 1 (6 7)	n.s.
Recovery time (min)	26.4 (8.8)	23 2 (8.8)	0.002
Time to home discharge (min)	136.9 (127 2)	136.6 (96.4)	n.s
Excitatory movement (*n*)	10	30	0 002

propofol/halothane group. There was no difference between groups in the time spent on the postoperative ward before discharge home. The incidence of excitatory movement during induction was significantly greater in the sevoflurane group. Twenty-two patients in the propofol group reported pain on injection. No differences were found between groups in the incidence of laryngospasm, breath-holding, or coughing during induction.

Although i.v. induction with propofol has been associated with a shorter induction time than sevoflurane in adults,[2] the longer recovery time may negate this advantage No differences were found between groups in time to discharge home. The incidence of pain on injection with propofol may make i.v. induction less pleasant for paediatric patients, whilst the restlessness already reported in adults during sevoflurane induction[3] may discourage anaesthetists from using this technique in children.

Acknowledgements. Funded by the National Co-ordinating Centre for Health Technology Assessment (UK).

Keywords: anaesthetic techniques, inhalation; anaesthetics volatile, sevoflurane; anaesthetics volatile, halothane

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The effects of glyceryl trinitrate and dobutamine on cerebral haemodynamics

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Glyceryl trinitrate (GTN) and dobutamine are often used in critically ill patients. Their effects on cerebral haemodynamics are not well established. We aimed to measure their effects on middle cerebral artery blood flow velocity (MCAFV), cerebral autoregulation (CA), cerebrovascular reactivity to carbon dioxide ($CRCO_2$), estimated cerebral perfusion pressure (eCPP), and critical closing pressure (CCP), as assessed by transcranial Doppler ultrasonography.

We recruited ten healthy volunteers, aged 24–40 yr. Study set up included continuous measurement of MCAFV, end-tidal carbon dioxide (PE'_{CO_2}) monitoring and non-invasive arterial pressure measurement. Baseline values of mean (MAP) and diastolic arterial pressure (DAP), and systolic, mean and diastolic MCAFV's were recorded. CA was assessed by performing a transient hyperaemic response test and calculating the strength of autoregulation (SA).[1] CR_{CO_2} was assessed by measuring MCAFV after induced changes in PE'_{CO_2} and calculated as per cent change in MCAFV per kPa change in PE'_{CO_2}.[1] These measurements were then repeated after the MAP was increased to a target of approximately 25% above the baseline value with an infusion of dobutamine, or, on a separate occasion, decreased by target of approximately 25%, with an infusion of GTN. Estimated cerebral perfusion pressure was calculated as: $MCAFV_{mean} \times [(MAP - DAP)/(MCAFV_{mean} - MCAFV_{diastolic})]$.[2] Critical closing pressure was calculated as: MAP − eCPP.[2] Paired *t*-test was used to compare these parameters before and after dobutamine, and before and after GTN infusion (Table 16).

Dobutamine increased MAP by 19%, eCPP by 10 mm Hg and CCP by 7 mm Hg, suggesting an increase in vessel tone. There was no significant change in MCAFV, SA, or $CRCO_2$. GTN decreased MAP by 13%, and CCP by 31 mm Hg, whilst increasing eCPP by 19 mm Hg. MCAFV decreased by 17%. Both SA and $CRCC_2$ were preserved.

Keywords. brain, blood flow; sympathetic nervous system, dobutamine; sympathetic nervous system, glyceryl trinitrate

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Attempting to estimate the rate of perfusion of the cerebral site of action of sevoflurane

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Table 16 Cerebrovascular haemodynamic parameters (mean (SD)) *$P<0.05$

	Pre-dobutamine	Post-dobutamine	Pre-GTN	Post-GTN
MAP (mm Hg)	89 (9)	106 (8)*	83 (5)	72 (4)*
MCAFV(cm^{-1})	52 (11)	56 (13)	52 (12)	43 (10)*
SA	41 07 (0 15)	1.03 (0 19)	1 14 (0.21)	1 31 (0.2)
$CRCO_2$ (%kPa^{-1})	37 (12)	37 (11)	37 (9)	43 (8)
ECPP (mm Hg)	53 (14)	63 (11)*	44 (13)	63 (18)*
CCP (mmHg)	36 (14)	43 (10)*	38 (10)	9 (15)*

Finding out how and where anaesthetics act in the brain remains an important area of research. As neuronal activity is closely coupled to glucose metabolism and cerebral blood flow, attempts have been made to use positron emission tomography (PET) to identify sites of anaesthetic action within the brain.[1]

An alternative approach has been to use the time to unconsciousness (defined here as failure to respond to an auditory stimulus) during a controlled inhalation induction to estimate the rate of perfusion of the cerebral site or sites involved. The data in the literature are not entirely satisfactory for this purpose[2] and we have, therefore, conducted a series of cases in an attempt to improve the accuracy of this estimation.

Fifteen patients of ASA class I–II aged 16–65 yr undergoing minor day case surgery were studied. An electronic metronome set to give a bleep at 1-s intervals was placed on the pillow during induction and patients were asked to press a button in response to each bleep. The method was explained to each patient and the bleep demonstrated at the preoperative visit.

Induction was by 8% sevoflurane in oxygen via a co-axial system with a 5 litre reservoir bag. Breathing was controlled by the exhortations of the anaesthetist to be a series of deep breaths. This was found to be more consistent than the vital capacity method. Tidal volumes and inspired and expired sevoflurane concentrations (from a Datex AS3 monitor) were recorded using a chart recorder. The bleeps and responding button presses were also recorded on the chart so that the time from start to cessation of response could be easily measured.

We assumed that the arterial anaesthetic tensions equalled the end-expired partial pressures and that the rate of increase of anaesthetic tension in the site of interest was proportional to the difference in tension between that site and arterial blood. The constant of proportionality, k, is the quotient of the perfusion and the tissue/blood partition coefficient. For convenience we fitted an arbitrary continuous function to the end-expired data that then allowed accurate numerical calculation of the tension at the site of interest for any value of k. The value of k was varied to obtain a tissue tension of 0.78% (MAC$_{awake}$) at the time of loss of response. Assuming a tissue/blood partition coefficient of 1.7, we calculated the perfusion from this value of k. Allowance was made for transit time between lung and brain

The mean time taken to unconsciousness for the 15 patients studied was 43.9 s (95% CI 38–45). The mean calculated perfusion rate was 82 ml 100 g^{-1} min^{-1} (median (95% CI) 76 (61–95)).

Keywords: anaesthetics volatile, sevoflurane; brain

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POSTER PRESENTATIONS

A nested case-controlled study of risk factors for perioperative cardiovascular death

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We have reported a nested case-controlled study of risk factors associated with cardiac death within 30 days of general anaesthesia in patients undergoing elective non-cardiac surgery. The study examined patients undergoing surgery between 1979 and 1990, identifying arterial hypertension, preoperative renal impairment (serum creatinine >200 mmol litre^{-1}) and a past history of myocardial infarction as risk factors associated with perioperative cardiac death.[1] However, the past decade has seen advances in the management of cardiovascular disease and perioperative care. We have, therefore, conducted a further case-controlled study using data for the period 1991–1998 to examine the possible impact of these changes.

Oxford Record Linkage Study database of medical records was interrogated to identify patients aged more than 16 yr who died from cardiovascular causes within 30 days of non-cardiac and non-neurological surgery [1] Patients were matched with controls for the same surgeon and operation, and age±10 yr. The notes of the cases and controls were examined, the certified cause of death confirmed, and data recorded on cardiac risk factors, intercurrent medications and perioperative investigations.

Eighty-three cases were identified (23 vascular, 17 orthopaedic, 15 urological, and 28 abdominal surgery patients); 55 cases and 47 controls were male; and the age ranges were 62–91 and 60–89 yr, respectively Death occurred between days 0 and 29 (median day 8). Univariate analysis identified four risk factors associated with cardiac death: history of angina (OR 2.30, 95% CI 1.06–5.41); previous history of cardiac failure (OR 4.40, 1.63–14.87); treatment with diuretics (OR 2.42, 1.20–5.20), or nitrates (OR 15.0, 2.31–631.43) Multivariate analysis was then performed using logistic regression Risk factors were included in the model if they achieved significance at the 5% level. Automated modelling procedures were not used. To allow for comparison with other previous studies, adjustment was made for sex and for residual confounding by age. When clinical risk factors were examined, but data on intercurrent medication excluded, cardiac failure (OR 4.27, 1.60–11.38) was the only significant risk factor in the model. When data on drug therapy were included in the modelling process, it was found that treatment with nitrates was a significant factor and treatment with diuretics could be substituted for cardiac failure. These gave a model with an OR of 15.77 (2.02–122.75) for nitrates, and OR of 2.87 (1.30–6.30) for diuretics as risk factors for perioperative cardiac death.

These data should be interpreted with caution. However, they would support an impact of changes in the treatment of intercurrent disease on the occurrence of perioperative complications. In contrast to our earlier study,[1] we have shown no association between past histories of myocardial infarction or arterial hypertension, or renal impairment and cardiac death. Several factors may account for these differences: different and more potent intercurrent drug therapies for cardiac diseases, better perioperative arterial pressure control, and better monitoring in the intra- and immediate postoperative periods

Keywords: complications, perioperative death; risk factors

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Methylprednisolone administration reduces renal proximal tubular injury during cardiac surgery

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Significant renal tubular dysfunction, measured using urinary *N*-acetyl-β-D-glucosaminidase (NAG), has been documented after cardiac surgery with cardiopulmonary bypass (CPB) [1] Large

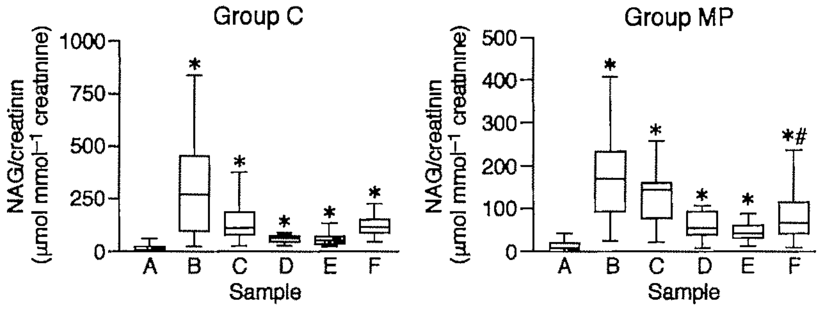

Fig 5 NAG/creatinine ratios in group C (n=17) and group MP (n=16). Box and whisker plots show median, 25th and 75th percentiles and range. *P<0.01 within group compared with baseline. #P<0.05 between groups Note difference in scale between C and MP groups

increases in urinary anti-inflammatory cytokines are observed at CPB implying their production in the kidney, in response to glomerular filtration of plasma pro-inflammatory cytokines.[2] Urinary IL-1ra concentrations have been shown to correlate with proximal renal dysfunction as indicated by NAG production.[2] Methylprednisolone reduces the plasma pro-inflammatory response during cardiac surgery and is accompanied by a reduction in urinary anti-inflammatory cytokines.[3] [4] This study investigated whether methylprednisolone administration would reduce proximal tubular dysfunction.

Thirty-three ASA grade III–IV patients undergoing elective coronary artery bypass grafting were allocated randomly to receive methylprednisolone 30 mg kg^{-1} before induction (group MP) or placebo (group C). Urine samples were obtained for NAG and creatinine measurement as follows: baseline (sample A), after cross-clamp release (sample B), and 2, 6, 24, and 48 h post-CPB (samples C, D, E, and F, respectively). Results were analysed using non-parametric repeated measures analysis of variance with Dunn post-test or Wilcoxon signed rank and Mann–Whitney test as appropriate.

Urinary NAG/creatinine ratios increased significantly in both groups over the study period (P<0.01) compared with baseline (Fig. 5). The increase demonstrated in Group MP was significantly lower in comparison to group C at 48 h post-CPB (P<0.05).

These findings would suggest that the renal injury in the methylprednisolone group was of a lesser magnitude and shorter duration than that in the control group, indicating that methylprednisolone may provide some degree of protection against renal dysfunction after cardiac surgery. The exact mechanisms involved require further investigation.

Keywords: surgery, cardiovascular; complications, renal damage

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Does end-tidal carbon dioxide affect speed of induction of anaesthesia with propofol?

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Kinetic models suggest that the rate limiting factor of anaesthetic induction for i.v. anaesthetic agents is the delivery of the agent to the brain.[1] Increased cerebral blood flow enhances the cerebral uptake of anaesthetic agents.[2] Increasing arterial carbon dioxide partial pressure (Pa_{CO_2}) increases cerebral blood flow.[3] The increased cerebral blood flow associated with hypercapnia should, thus, increase anaesthetic delivery to the brain and could reduce induction time. Hypercapnia can be induced in the anaesthetic room by rebreathing from a Bain circuit.[4] We studied how rebreathing affected induction time with propofol.

We allocated randomly 47 healthy patients undergoing minor gynaecological procedures to breathe from a Bain circuit supplied with either a low (2 litre min^{-1}) or high (12 litre min^{-1}) flow of oxygen. Oxygen breathing started 1 min before the infusion and continued throughout induction. To give the agent at a comparable rate in different subjects, we estimated the induction dose of propofol from age and weight, diluted 1.6 times this dose into 40 ml, and gave it i.v. at a rate of 5 ml min^{-1}. In this way, the mean time to induction would be 300 s. Induction time was measured from start of infusion to the time an outstretched arm came down from 45° to horizontal. Time to induction was compared with Student's t-test, and P<0.05 was considered significant. Values are given as mean (SD).

The patient groups were comparable (low flow (n=24): age 29 yr (range 16–51), weight 64 kg (8), height 165 cm (7); high flow (n=23): age 27 yr (15–45), weight 63 kg (9), height 164 cm (5)). $F\text{E}'_{CO_2}$ increased by 1.3% (0.4%) and decreased by 0.1% (0.6%) during low and high flow induction (P<0.001). Mean times to induction of anaesthesia were 184 (54) and 202 s (46) for low and high flow, respectively (P=0.216). There is no correlation between $\text{D}F\text{E}'_{CO_2}$ and time to induction (Fig. 6). The power of the study, to show that a slow i.v. injection of propofol will act 25% more rapidly when rebreathing is encouraged, is 0.94. A possible explanation for our findings could be a parallel increase in cardiac

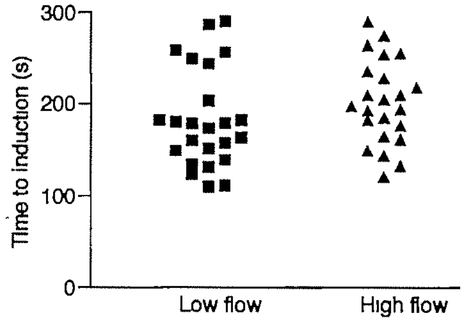

Fig 6 Time to induction with low and high fresh flow.

output and thus a similar rate of delivery of propofol to the brain in the two groups.

Keywords: anaesthetic techniques, induction, ventilation, rebreathing

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Interaction of i.v. anaesthetic induction agents with recombinant human m1–m3 muscarinic receptors expressed in Chinese hamster ovary cells

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Previous reports suggest that the effects of i.v. anaesthetic agents propofol, ketamine, and thiopental on airway tone may result from parasympathetic modulation.[1 2] In the present study, we examined if these agents interact with human m1–m3 muscarinic receptors stably expressed in Chinese hamster ovary cells (CHO-m1, m2, and m3, respectively).

Receptor interaction was determined by displacement of 1-[*N*-methyl-^{3}H]scopolamine methyl chloride ([^{3}H]NMS) binding. CHO-m1, m2, and m3 cell membranes (*n*=5–10) were incubated in buffer containing approximately 0.4 nM [^{3}H]NMS and thiopental, propofol (10^{-6}–10^{-3} M), ketamine (10^{-5}–10^{-2} M) and non-anaesthetic barbiturate, barbituric acid (10^{-6}–10^{-3} M) as described previously.[3] In addition, as an index of receptor function, intracellular Ca^{2+} ($[Ca^{2+}]_i$) was measured fluorometrically in fura2 loaded whole cells stimulated with 1 mM methacholine.[4]

Ketamine dose-dependently displaced [^{3}H]NMS binding to CHO-m1, m2, m3 membranes with pK_i (mean (SEM)) values of 4.34 (0.14), 3.53 (0.10), and 3.61 (0.02), respectively. However, ketamine did not affect either basal or methacholine stimulated increase in $[Ca^{2+}]_i$ in CHO-m1 cells (m2 and m3 were not used as the interaction in binding was weak). Thiopental significantly displaced [^{3}H]NMS binding to m3 (but not m1 or m2) with a pK_i of 4.12 (0.06) In addition, thiopental (10^{-5}–10^{-3} M) dose-dependently inhibited methacholine stimulated increase in $[Ca^{2+}]_i$ in CHO-m3 cells. Propofol and barbituric acid were inactive at m1, m2, and m3

We conclude that thiopental may act as an m3 antagonist, while ketamine and propofol are likely to be functionally inactive at airway muscarinic receptors.

Keywords: anaesthetic techniques, i.v.; parasympathetic nervous system, recombinant muscarinic receptors

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The effect of moxifloxacin on release of interleukin-8 from human neutrophils

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Interleukin 8 (IL-8) is a neutrophil chemotactic and activating factor produced in response to inflammatory stimuli including lipopolysaccharide (LPS). Although IL-8 has a major role in the host response to infection via recruitment and activation of neutrophils, increased concentrations are associated with poor outcome. We have previously shown that the fluoroquinolone antibiotic ciprofloxacin increases IL-8 mRNA expression and IL-8 protein release in endothelial cells.[1 2] Although moxifloxacin (Avelox, Bay 12–8039, Bayer Plc) has a similar mechanism of action to ciprofloxacin, it is structurally different and its immunomodulatory effects are unknown. We investigated the effect of moxifloxacin on IL-8 release from stimulated human neutrophils.

Neutrophils were isolated from 20 healthy volunteers aged 20–47 yr, using single density gradient centrifugation, and incubated with 2 µg ml^{-1} LPS plus 0–50 µg ml^{-1} moxifloxacin at 37°C in 95% air/5% carbon dioxide for 20 h. IL-8 was measured in cell culture supernatants using enzyme immunoassay Data are expressed as median (range) and were analysed using Friedman analysis of variance and Wilcoxon signed rank tests.

Although IL-8 release was variable between subjects, release of IL-8 increased in all cases from 19.5 (0.9–225.9) to 37.9 (1.8–387.0) pg ml^{-1} on exposure to LPS (*P*=0.05). In cells also treated with moxifloxacin, IL-8 release decreased with increasing concentrations of the antibiotic (*P*=0.02) and levels were significantly lower than in the absence of moxifloxacin at all concentrations (*P*<0.05, Fig. 7) Exposure to moxifloxacin had no effect on cell viability.

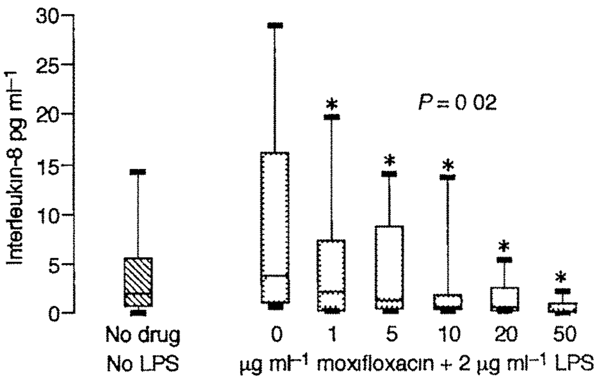

Fig 7 Effect of moxifloxacin on IL-8 release from human neutrophils stimulated with 2 µg ml^{-1} LPS (*n*=20) Box and whisker plots show median, 25th and 75th percentile and range *P* value refers to Friedman analysis of variance. *Wilcoxon signed ranks test compared to cells not exposed to moxifloxacin, *P*<0.05

Moxifloxacin decreased LPS-mediated IL-8 release from human neutrophils, in contrast to our previous findings with ciprofloxacin. This implies that the structure of these antibiotics has a profound effect on their immunomodulatory properties and further studies are required.

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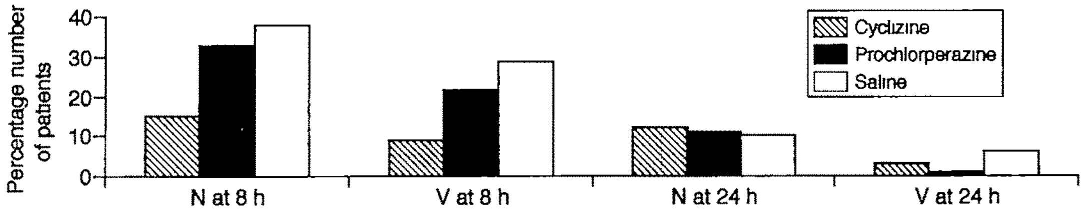

Fig 8 Incidence of PONV.

Keywords: antibiotics, moxifloxacin; immune response, interleukin-8

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Cyclizine reduces the incidence of nausea and vomiting after elective Caesarean section with intrathecal diamorphine

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Regional anaesthesia is now used for the majority of elective Caesarean sections in the UK, and intrathecal opioids are administered to allow both a reduction in the dose of local anaesthetic, whilst also providing postoperative analgesia Recognised side effects include postoperative nausea and vomiting (PONV). Audit in our unit revealed an incidence of 48%, with a reported incidence of up to 75%.[1] Our study compared the effectiveness of cyclizine, prochlorperazine, and placebo in reducing the incidence of PONV in women undergoing spinal anaesthesia with intrathecal diamorphine for elective Caesarean section.

We recruited 224 ASA I or II patients into the study The women received our standard spinal anaesthetic technique, and were randomized to receive either 50 mg cyclizine, 12.5 mg prochlorperazine, or 1 ml saline. This was given at the end of the procedure as an i.m. injection into the anaesthetized thigh. The patients were questioned on the ward at 8 and 24 h with regards to nausea, vomiting, and side effects, within these time periods. Data were collected and analysed on SPSS version 9 for Windows©, and a chi-squared test was performed on all PONV data. A P-value of <0.05 was considered statistically significant.

Eight patients were excluded (four in the cyclizine, one in the prochlorperazine, and three in the placebo group). Three were excluded because of severe PONV in recovery requiring i.v. ondansetron, three were lost to follow-up, one withdrew consent before injection, and one was sedated and ventilated after postoperative complications unrelated to the study. Groups were comparable with respect to age and obstetric history. Results are shown in Figure 8. In the first 8 h after the Caesarean section, the incidence of PONV was significantly reduced in the cyclizine group when compared with the prochlorperazine and placebo groups. In the subsequent 16 h, the incidence of PONV was similar in all three groups.

The requirements for supplementary antiemetics, and reported side effects, were similar between the three groups.

Keywords: vomiting, antiemetics, cyclizine; anaesthesia, obstetric; vomiting, nausea

Reference

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Local anaesthetic and opioid drug absorption within epidural filters

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Drug binding and bacterial challenge[1] testing is an essential part of evaluating new epidural filter membranes before clinical use. The aim of this study was to assess potential drug absorption by a new epidural filter membrane after infusions of commonly used local anaesthetic and opioid drugs utilizing a previously established *in vitro* model capable of detecting small amounts of drug binding to filters. The sensitivity of the model was facilitated using drug concentrations much lower than that clinically administered.

Three batches of four drug solutions (bupivacaine $25\,\mu g\,ml^{-1}$; ropivacaine $100\,\mu g\,ml^{-1}$; fentanyl $2\,\mu g\,ml^{-1}$; diamorphine $80\,\mu g\,ml^{-1}$) were used to test 12 SIMS Portex epidural filters ($0.2\,\mu m$, polysulphone membrane filter). A sample (60 ml) of each solution in a BD Plastipak syringe was infused through a single filter at $10\,ml\,h^{-1}$ using an IVAC P1000 syringe pump. Drug concentrations, sampled both before and after the epidural filter at

Table 17 Drug absorption time course

Drug (% mean (SD))	0 min	15 min	30 min	45 min	60 min
Bupivacaine$_{\text{pre-filter}}$	100	99.71 (0 56)	100 07 (0 56)	100.37 (0.12)	100 36 (0.12)
Bupivacaine$_{\text{post-filter}}$	–	100.46 (0 29)	100 46 (0 28)	99 99 (0.94)	100 21 (0 46)
Ropivacaine$_{\text{pre-filter}}$	100	100.22 (0 23)	100 21 (0 13)	100 14 (0.06)	100 01 (0.09)
Ropivacaine$_{\text{post-filter}}$	–	100.03 (0.90)	100 15 (0 45)	99 84 (0.25)	100 01 (0.11)
Fentanyl$_{\text{pre-filter}}$	100	98.79 (0.54)	99 80 (0 41)	100.33 (0.73)	99.74 (1 06)
Fentanyl$_{\text{post-filter}}$	–	100 57 (0 72)	100 56 (0 72)	98.97 (0.59)	100 09 (0 22)
Diamorphine$_{\text{pre-filter}}$	100	99.69 (0 27)	99 92 (0 08)	100 17 (0 68)	100 26 (0 39)
Diamorphine$_{\text{post-filter}}$	–	99.96 (0 74)	99.96 (0.74)	100 33 (1 19)	99.49 (0 09)

predetermined time intervals (0, 15, 30, 45, 60, 120, 180, and 240 min), were measured using HPLC (high performance liquid chromatography) with a diode array detector. Samples were assayed in triplicate against a freshly prepared drug reference solution. Data were expressed as mean (SD) percentage (%) drug concentration with each pre-filter value compared with pre-filter at time, 0 min (control) and each post-filter value compared with its corresponding pre-filter value. A saline infusion through a test filter was also included in the procedure as a negative control. Statistical analysis included the Shapiro–Wilk test and repeated measures ANOVA using a general linear model ($P<0.05$).

No statistically significant differences ($P=0.998$) were observed in mean % drug concentration, for all drugs, over the initial 60 min-testing period (Table 17), when empirically maximal initial drug absorption would be expected to occur. No further significant differences were observed up to the total testing period of 240 min.

These experiments demonstrate no drug absorption by the epidural filter membrane over the 240 min test period.

Acknowledgements: SIMS Portex Ltd for study funding and Research Fellowship (VS).

Keywords: equipment, epidural filter membrane

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Are training standards for general anaesthesia in obstetrics impossible to meet?

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In the year 2000, there were 860 Caesarean sections at Northwick Park Hospital. General anaesthesia was used in 124 cases and they were classified[1] into 53, 38, 20, and 13 for types 1, 2, 3, and 4 Caesarean section, respectively. Eighty-four operations were outside normal operating hours. Analysis of the grades of the principal anaesthetist for general anaesthesia were consultant (19 cases), staff grade (eight), year 1–2 SPR (93), and year 3–4 SPR (four). Twenty-one cases had two or more anaesthetists present. Year 1–2 SPRs were with a senior anaesthetist for 16 Caesarean sections and performed 93 alone or with an SHO. During 2000, eight year 3–4 SPRs were in the department—six performed no general anaesthetics for Caesarean section, one performed two, and one performed 1. There were 12 year 1–2 SPRs. All 12 performed between two and 13 general anaesthetic Caesarean sections (mean 8). There were six anaesthetists at SHO level—four were present at six general anaesthetics whilst two did not see any. There were 102 grade 1, 15 grade 2, seven grade 3, zero grade 4, and no failed intubations.

The OAA recommends a minimum experience of 20 obstetric general anaesthetics in training and that training should primarily take place in the SHO grade and be of 8 weeks duration. These current recommendations are impossible to meet and the guidelines should be amended. Training takes place primarily in the year 1–2 SPR grade and supervised training is difficult. It is important that trainees be given adequate training in all theatre situations so that laryngoscopy grade 3 and failed intubation can be managed successfully. Grade 3 intubations are generally reported as 1.7% and in our unit are 1.6%. Failure of expertise has accounted for both of the failed intubations that have occurred in our unit over the past 5 yr. Will the incidence of general anaesthesia mortality increase from zero as in the last Confidential Enquiry into Maternal Mortality (1994–1996) report as a result of less experienced trainees and consultants emerging from training?

Keywords: anaesthesia, obstetric; education

Reference

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Dural puncture and subsequent blood patches in the obstetric population

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Post-dural puncture headache is a recognised complication of spinal and epidural anaesthesia. Epidural blood patch is the accepted treatment of persistent headache though debate exists as to its success.[1 2] A retrospective audit of all epidural blood patches performed in the Rotunda Hospital over a 4-yr period from 1996 to 2000 was perfomed. The aim was to examine the efficacy of epidural blood patches in the management of post-dural puncture headache and to identify any risk factors to the development of severe post-dural puncture headache.

Theatre records for the 4-yr period were examined and the charts of all patients who had blood patches performed during this period were reviewed. Date, time, seniority of anaesthetist, patient characteristics, position and size of needle used were recorded. In addition, time to onset of symptoms, time to blood patch insertion, symptom relief, need for subsequent blood patch, and symptoms on discharge were all noted. Patients were then sent a questionnaire to complete and return enquiring about symptoms on their return home and whether they would have a repeat epidural for subsequent deliveries. Non-responders were subsequently contacted by phone.

During the study period 15 088 epidurals and 3622 spinals were performed. Eighty-seven patients required blood patches, 61 (70.11%) after accidental dural puncture and 26 (29.88%) after spinal anaesthesia. Of these 11 (12.64%) needed repeat blood patches. The combined response rate was 72.09%. The majority of the procedures were performed by junior anaesthetists (SHO 75.86%). Headache reoccurred in 33 patients (53.22%) on discharge and new backache was present in 33 (53.22%) of patients questioned. The majority of patients would not have a repeat epidural (50 *vs* 33.87%) while 16.13% were unsure.

Epidural blood patches are not as effective in the long-term treatment of post-dural puncture headaches as thought. Dural puncture headache causes considerable morbidity in the obstetric patient, leading to long-term symptoms in a large proportion of the patients surveyed. The majority of those surveyed would not have an epidural again.

Keywords: complications, dural puncture headache; complications, epidural blood patch

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Diagnosis of occiput-posterior position from failure of epidural analgesia in the first stage of labour

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Occiput-posterior (OP) position of the fetus is associated with long, difficult labours, and with failure of epidural analgesia.[1] In early labour, OP position can be difficult to diagnose, but becomes easier with descent of the head. In the majority, the fetal head rotates via occiput-transverse (OT) to an occiput-anterior (OA) position, but the malposition may persist in 6–8%.[2] The aim of this study was to assess if the pattern of pain distribution in women, whose epidural analgesia was inadequate, could be used to diagnose OP fetal position.

A 3-month prospective observational study was designed to identify labouring women with failure of epidural analgesia and the associated fetal position. Failure of epidural analgesia was defined as unacceptable pain, as assessed by the attending midwife, at least 30 min after an initial bolus of 20 ml of 0.06, 0.08, or 0.1% bupivacaine plus 20 μg ml^{-1} alfentanil, followed by a 12 ml h^{-1} infusion. An epidural failure was, therefore, one that required a concentration of bupivacaine greater than 0.1% at any time throughout its use. The anaesthetist assessed the pain distribution pattern as either abdominal or lower back, rectal, with premature pushing urge, and decided on the pain rescue options: increased concentration of local anaesthetic bolus, re-site the epidural or combined spinal epidural anaesthesia. The fetal position was assessed by a midwife using vaginal examination or abdominal palpation. The duration of epidural analgesia was calculated.

Twenty-six women with failure of epidural analgesia were identified from a total of 462 (5.6%). Three women had incomplete data, leaving 23 for analysis. Nineteen women were nulliparous. The initial rescue medication administered was stronger local anaesthetic bolus +/− opioid in 22 cases, one epidural was re-sited immediately for a unilateral block. Four epidurals subsequently required re-siting after ineffective rescue medication, including two in combination with a spinal anaesthetic. All re-sites were effective. The pain distribution pattern, fetal position, and duration of epidural analgesia are recorded in Table 18. Back pain, as a test of OP position is 86% sensitive, but only 69% specific. Its negative predictive value is 92%.

We conclude that, in women requiring rescue medication for inadequate pain relief in the first stage of labour, OP position of the fetus is significantly associated with back pain, rectal pressure and prolonged epidural analgesia. Clinically, abdominal pain in a woman with inadequate epidural analgesia is unlikely to be associated with OP position of the fetus, and may be useful for its negative predictive value.

Keywords: anaesthesia, obstetric, complications, fetal position

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Table 18 Pain distribution pattern and duration of epidural analgesia

Fetal position	**Pain distribution pattern**		**Mean duration of epidural analgesia in min (SD)**
	Back or rectal pain/pushing urge	**Abdominal pain only**	
OP	6	1	451 (104)
OA/OT	5	11	312 (150)
	Fisher's exact test P=0.027		Student t-test P=0.038

An audit of high dependency care for obstetric patients in the Yorkshire region

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The latest Confidential Enquiry into Maternal Deaths[1] recommended the establishment of High Dependency Units (HDUs) for the care of the high-risk obstetric patient. Before an Obstetric HDU course being held at Leeds General Infirmary in November 2000, an audit was conducted to gain a picture of HDU provision and midwife training in the Yorkshire region. Participants at the course were then asked about their own training and practical experience in the management of the high-risk obstetric patient and their confidence in the management of various situations.

A questionnaire was sent to the midwife-in-charge of each delivery unit in the Yorkshire region. Thirty questions were asked regarding the availability of HDU facilities at their unit and training provided for midwives in HDU care. Participants attending a local HDU course were also asked to complete a two-part questionnaire at the start of the first session; the first part questioned their background experience and the second asked midwives to complete a 1–10 visual analogue rating of their subjective confidence in the management of eight common situations.

Questionnaires were sent to 18 units and 16 forms were returned (89% response rate). The majority of units (14/16) nursed patients requiring HDU care on the delivery suite, but only four units (22%) had a dedicated HDU and only five units (28%) made specific reference to the availability of basic monitoring facilities. HDU training was provided by only a minority of units; two units had an HDU training programme and six units had a study day or an HDU/ITU experience day. Midwives in half of the units felt they would benefit from more training in the care of HDU patients, with anaesthetic department input being specifically mentioned. The HDU course participants' confidence ratings were higher in areas that specifically related to obstetric problems (median (range)VAS: epidural complications 9 (2–10) and pre-eclampsia 9 (1–9)) and lower in those relating to monitoring of the mother (basic monitoring 6 (1–10) and invasive monitoring 4 (1–10)), major haemorrhage 7 (1–10) and management of the collapsed mother 6 (1–10). Despite limited exposure to patients recovering from general anaesthesia, with the greater use of regional techniques for operative delivery, midwives felt confident with postoperative recovery 9 (2–10). As regards their training and experience, although many of the course participants (77%) had nursed mothers requiring high dependency care on a delivery suite, the majority (92%) had never worked in a general HDU or ITU or received formal HDU training. Anaesthetic-led teaching for midwives is uncommon on either HDU issues or even routine anaesthetic techniques and their complications.

It is evident that the majority of units in our region are managing high-risk obstetric patients with inadequate facilities,

Table 19 Mean or median anxiety scores (range). *$P<0.0001$ Mann–Whitney (paired), each group, between admission and anaes rm **$P=0.057$ (ns) Mann–Whitney (paired), group 1, between admission and anaesthetic room Admiss., admission; Anaes rm, anaesthetic room

	Group 1		**Group 2**		**Group 3**	
	Admiss.	**Anaes. rm**	**Admiss.**	**Anaes. rm**	**Admiss.**	**Anaes. rm**
Number	44		45		35	
Mean LAAS	4.32	5.53*	3.79	5.88*	4.42	6.59*
(0–10) (range)	(0–9.5)	(0–10)	(0–9.8)	(0.2–10)	(1–8.5)	(2.2–10)
Median HAD	8	9**	–	7.5	8	–
(0–21) (range)	(0–18)	(0–21)	–	(0–20)	(1–17)	–

staffed by midwives with inadequate training and clinical experience in HDU care. It is also evident that although anaesthetists are increasingly involved in the peripartum care of sick mothers, midwives are not receiving the benefit of our knowledge and expertise. There is, therefore, an urgent need for increased anaesthetic input into the training of midwives generally and HDU care specifically.

Keywords: anaesthesia, obstetric; high dependency care

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Linear analogue anxiety scale or hospital anxiety and depression score to assess preoperative anxiety in day case surgery

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In a previous study presented to the Society, we used a Linear Analogue Anxiety Scale (LAAS) to measure preoperative anxiety.[1] However, a more established measure is the questionnaire-based Hospital Anxiety and Depression Score (HAD).[2 3] LAAS and HAD have been compared preoperatively,[3 4] but not immediately before induction of anaesthesia. We used only the seven anxiety-orientated questions of the HAD,[3] which gives a maximum possible score of 21.

We recruited day case gynaecological patients as a model of increasing stress, randomized into three groups. Group 1 were given both tests on admission and in the anaesthetic room, group 2 only LAAS on admission but both in the anaesthetic room, and group 3 both tests on admission but only LAAS in the anaesthetic room. This allocation was intended to identify any learning component of the HAD questions. One hundred and twenty nine patients were recruited; 124 had sufficient data completed to be included in the analysis.

As in our previous study, virtually all LAAS scores increased between admission and the anaesthetic room. This increase was highly significant in all three groups ($P<0.0001$, paired Mann–Whitney). However, in group 1 (the only group to have HAD on both occasions) the HAD score increased in only 26 of 35 patients who completed both tests, and the increased median score did not reach statistical significance. Several patients did not in fact complete the HAD in the anaesthetic room as they were too anxious! There was however a statistically significant but weak correlation between LAAS and HAD for all groups combined (Spearman $r=0.48$ 95% CI 0.32–0.61, $P<0.0001$) (Table 19).

We suggest that LAAS is a more reliable and sensitive tool for measurement of anxiety than HAD in a preoperative day case setting, particularly when more than one assessment needs to be made in quick succession.

Keywords. psychological responses, preoperative anxiety

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Monographs:

3. Moore, DC. *Regional Block,* 4th Edn Springfield, Illinois· Charles C. Thomas, 1979

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We interrupt this to bring you a very important message:
By the time you've read this, someone will have died from sepsis.

Recent analyses conducted by ICNARC (the Intensive Care National Audit & Research Centre) on data collected from 92 adult general ICUs[†] have shown that the prevalence of severe sepsis[‡] during the first 24 hours in the ICU is 27.7%[‖1]. In England and Wales (excluding Northern Ireland and Scotland), this figure potentially represents a prevalence of 21,033[‖1] severe sepsis cases during the first 24 hours in the ICU out of a total adult general ICU caseload of 73,203[‖1].

Severe sepsis is a major cause of morbidity and mortality. In adults, severe sepsis has been associated with mortality rates ranging from 28% to 50%[2] and these rates have remained unchanged for several decades. For the 92 adult general ICUs included in the Case Mix Programme Database, the associated overall hospital mortality for severe sepsis in England, Wales and Northern Ireland is 44.7%[‖1].

Lilly Critical Care continues to invest extensively in research to find better ways to manage sepsis.

References
1. Eli Lilly and Company Data on file Source of data The Intensive Care National Audit & Research Centre 2. Natanson C et al Crit Care Med 1998,26 1927–31

† throughout England, Wales and Northern Ireland, ‡ defined as sepsis associated with acute organ dysfunction, ‖ these figures do not include cases of severe sepsis that occur either on wards or after the first 24 hours in the ICU

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PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib. Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension. Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib. Rofecoxib may mask fever. Use of rofecoxib is not recommended in women attempting to conceive. In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB. At chronic daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased. Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib. Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated. *Interactions (pharmacodynamic): Warfarin:* closely monitor the prothrombin time INR when therapy with
rofecoxib is initiated or changed in patients receiving warfarin or similar agents, particularly
first few days. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril,
to 40 mg daily for four weeks to patients with hypertension was associated with a small attenu
of the antihypertensive effect compared to the ACE inhibitor alone. This should be consider
patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* concon
use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the
effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once daily had no effect on the
platelet activity of low-dose (81 mg once daily) aspirin. Avoid concomitant administration of ro
with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal function
rofecoxib and either cyclosporin or tacrolimus is used in combination. *Interactions (pharmacokin*
Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider ade
monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are adminis
concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxib
drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zileu
Midazolam: a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg
most likely due to increased first pass metabolism through induction of intestinal CYP3A4 act
by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activity
pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected
clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4

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xib. *Rifampicin:* co-administration of rofecoxib with rifampicin, a potent inducer of CYP es, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, er the highest dose when rofecoxib is used with potent inducers of hepatic metabolism. Based *itro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1. *ancy:* Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis ors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib not be used during the first two trimesters of pregnancy unless the benefit to the patient ghs the risk to the foetus. *Lactation:* contra-indicated.

EFFECTS

llowing drug-related undesirable effects were reported at an incidence greater than 1% and r than placebo in analgesia clinical studies in patients treated with rofecoxib 50 mg or 25 mg o 5 days: dizziness, diarrhoea, diaphoresis, dyspepsia. The following drug-related undesirable s were reported at an incidence greater than placebo in osteoarthritis clinical studies in patients d with rofecoxib 12.5 mg or 25 mg for up to six months, or in post-marketing experience. *mon (≥1/100, <1/10); Uncommon (≥1/1000, <1/100); Rare (≥1/10,000, <1/1000); Very <1/10,000) and isolated cases]*

as a whole/site unspecified: *Common:* oedema/fluid retention, abdominal pain, dizziness. *mon:* asthenia/fatigue, abdominal distension, chest pain. *Very rare:* hypersensitivity reactions, ing angioedema, urticaria and anaphylactic/ anaphylactoid reactions. ***Blood and the lymphatic system disorders:*** *Common:* haematocrit decreased. *Uncommon:* haemoglobin decreased, erythrocytes decreased, leukocytes decreased. *Very rare:* thrombocytopenia. ***Cardiovascular system:*** *Common:* hypertension. *Very rare:* congestive heart failure. ***Digestive system:*** *Common:* heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia. *Uncommon:* constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux. *Rare:* peptic ulcers, gastro-intestinal perforation and bleeding (mainly in elderly patients), gastritis. ***Hepatobiliary disorders:*** *Common:* alanine aminotransferase increased, aspartate aminotransferase increased. *Uncommon:* alkaline phosphatase increased. *Isolated cases:* hepatotoxicity including hepatitis and jaundice. ***Eyes, ears, nose and throat:*** *Uncommon:* tinnitus. *Very rare:* blurred vision. ***Metabolism and nutrition:*** *Uncommon:* weight gain. ***Musculoskeletal:*** *Uncommon:* muscular cramp. ***Nervous system:*** *Common:* headache. *Uncommon:* insomnia, somnolence, vertigo. *Very rare:* paraesthesia. *Isolated cases:* aseptic meningitis. ***Psychiatric disorder:*** *Uncommon:* depression, mental acuity decreased. *Very rare:* confusion, hallucinations. ***Respiratory system:*** *Uncommon:* dyspnoea. *Very rare:* bronchospasm. ***Urogenital:*** *Uncommon:* BUN increased, serum creatinine increased, proteinuria. *Very rare:* renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy. ***Skin and skin appendages:*** *Common:* pruritus. *Uncommon:* rash, atopic dermatitis. *Very rare:* alopecia. *Isolated cases:* cutaneo-mucosal adverse effects and severe skin reactions including Stevens-Johnson Syndrome. In clinical studies, the undesirable effects profile was similar in patients treated with rofecoxib for one year or longer. The following serious adverse effects have been reported in association with the use of NSAIDs and cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome; hepatotoxicity including hepatic failure.

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EPREX® ABBREVIATED PRESCRIBING INFORMATION

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use: increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM.

Product licence/authorisation holder:
Janssen-Cilag Ltd, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK.
(PL/0242/0215, 0218, 0221, 0297-9 PA/748/25/1-9)

Date of preparation: February 2000

Further information: Available from:
Janssen-Cilag Ltd, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK.

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EPREX® (epoetin alfa) Increases Preoperative Haemoglobin Levels[1,2]

EPREX Maintains Higher Postoperative Haemoglobin Levels[1,2]

Higher Haemoglobin Results In
Reduction in transfusions[1,2]
Improved early postoperative vigour[3]
Earlier participation in rehabilitation[3]

EPREX Is Generally Well Tolerated

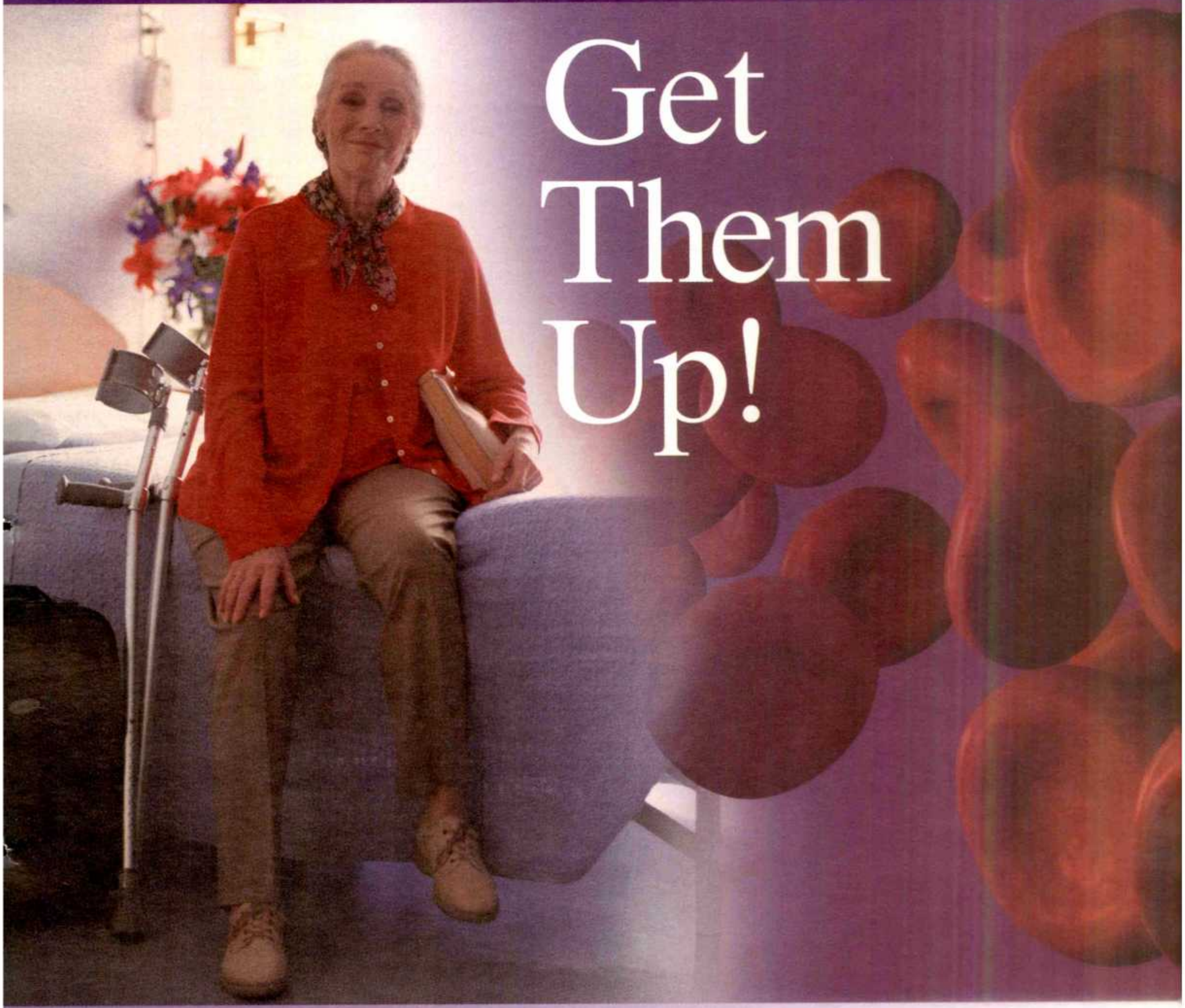
*Haemoglobin levels >10 to ≤13 g/dL.

References:
1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz MC. *Orthopedics.* 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

Please see abbreviated Prescribing Information on adjacent page.

In moderately anaemic patients scheduled for orthopaedic surgery*

HIGHER HAEMOGLOBIN LEVELS MAKE A DIFFERENCE



EPREX®
epoetin alfa

01133

Abbreviated version of the International summary of product characteristics Therapeutic indications*: Esmeron is indicated as an adjunct to general anesthesia to facilitate tracheal intubation during routine and rapid sequence induction, and to provide skeletal muscle relaxation during surgery. Esmeron is also indicated as an adjunct in the intensive care unit (ICU) to facilitate tracheal intubation and mechanical ventilation. **Contra-indications** Former anaphylactic reactions to rocuronium or to the bromide ion. **Special warnings and special precautions for use** Since Esmeron causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this drug until adequate spontaneous respiration is restored. As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique. Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Esmeron, have been reported. These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume that they may occur and take the necessary precautions. Dose levels greater than 0.9 mg rocuronium bromide per kg body weight may increase the heart rate; this effect could counteract the bradycardia produced by other anesthetic agents or by vagal stimulation. In general, following long term use of muscle relaxants in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of muscle relaxants. In addition, patients should receive adequate analgesia and sedation. Furthermore, muscle relaxants should be titrated to effect in the individual patients by or under supervision of experienced clinicians who are familiar with their actions and with appropriate neuromuscular monitoring techniques. Because Esmeron is always used with other agents and because the occurrence of malignant hyperthermia during anesthesia is possible, even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anesthesia. In animal studies, Esmeron was shown not to be a triggering factor for malignant hyperthermia. **The following conditions may influence the pharmacokinetics and/or pharmacodynamics of Esmeron:** *Hepatic and/or biliary tract disease and renal failure.* Because rocuronium is excreted in urine (up to approximately 30% within 12-24 hours) and it is expected that it is also partly excreted in bile, Esmeron should be used with caution in patients with clinically significant hepatic and/or biliary diseases and/or renal failure. In these patient groups prolongation of action has been observed with doses of 0.6 mg rocuronium bromide per kg body weight. *Prolonged circulation time.* Conditions associated with prolonged circulation time such as cardiovascular disease, old age and edematous state resulting in an increased volume of distribution, may contribute to a slower onset of action. *Neuromuscular disease.* Like other neuromuscular blocking agents, Esmeron should be used with extreme caution in patients with a neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or with the myasthenic (Eaton-Lambert) syndrome, small doses of Esmeron may have profound effects and Esmeron should be titrated to the response. *Hypothermia.* In surgery under hypothermic conditions, the neuromuscular blocking effect of Esmeron is increased and the duration prolonged. *Obesity.* Like other neuromuscular blocking agents, Esmeron may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients, when the administered doses are calculated on actual body weight. *Burns.* Patients with burns are known to develop resistance to non-depolarizing neuromuscular blocking agents. It is recommended that the dose is titrated to response. **Conditions which may increase the effects of Esmeron** Hypokalemia (e.g. after severe vomiting, diarrhea and diuretic therapy), hypermagnesemia, hypocalcemia (after massive transfusions), hypoproteinemia, dehydration, acidosis, hypercapnia, cachexia. Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible. Therapeutic indications may vary from country to country. *For full prescribing information see your local package insert. December 1999

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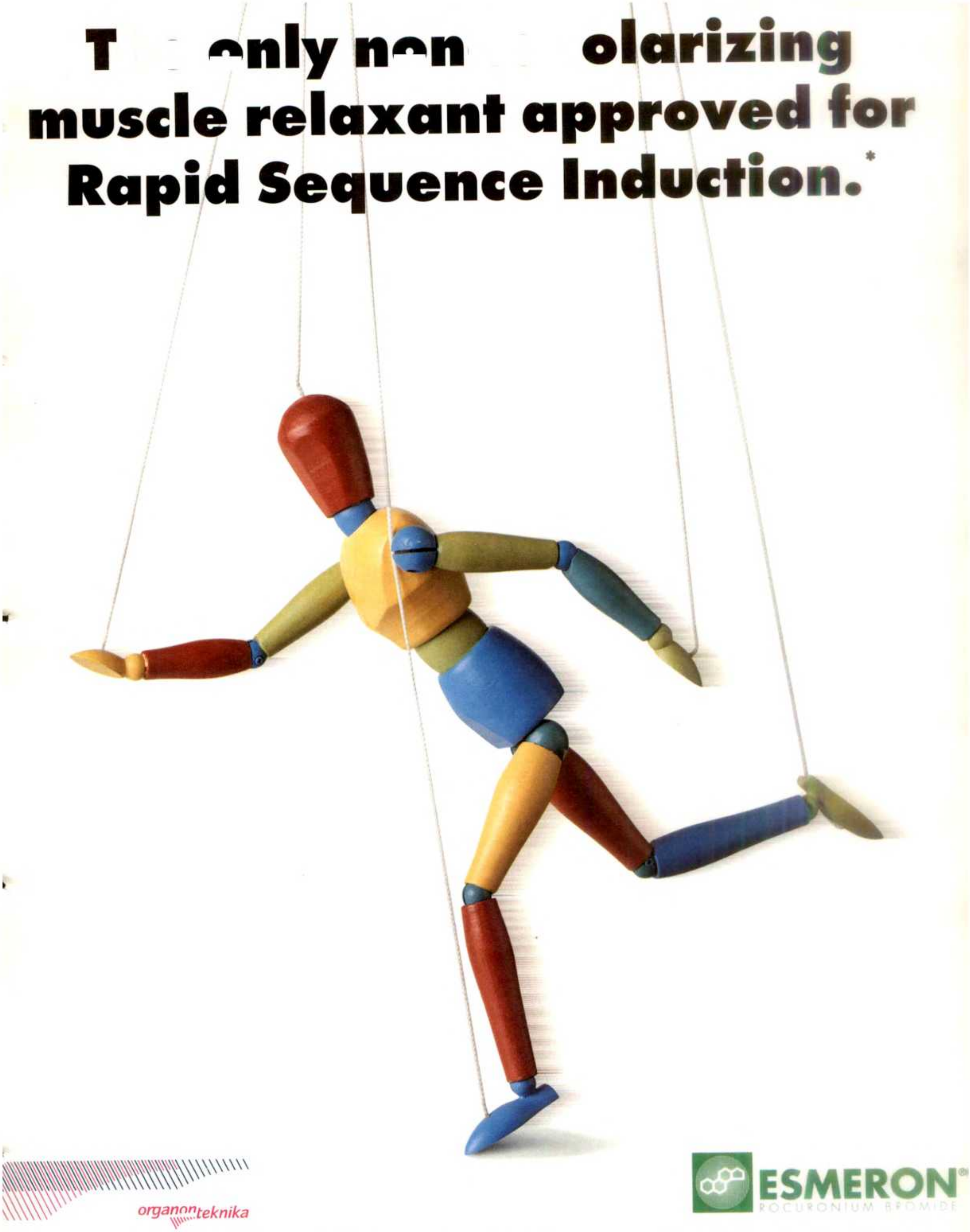
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* See local prescribing information.

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Editorial Notices

STRUCTURED ABSTRACTS

From January 2002, the Summary of all Clinical Investigations, Laboratory Investigations and Short Communications (but not Reviews, Case Reports or Commentaries) published in the *British Journal of Anaesthesia* will be structured under the headings:

Background
Methods
Results
Conclusions

All new manuscripts submitted to the *British Journal of Anaesthesia* from 1 May, 2001 should therefore be presented in this format. If an Editor asks for a revised version of a previously submitted manuscript, please change the Summary in your next draft to the new structured format.

Jennifer M. Hunter
Editor-in-Chief

Royal Medical Benevolent Fund

President's Christmas Message for 2001

Readers of the *British Journal of Anaesthesia*, in recent years, have been generous in their response to my Christmas Appeal on behalf of the Royal Medical Benevolent Fund.

Those of us involved in the work of the Fund are constantly made aware of colleagues or their dependents whose lives have been torn asunder by unexpected tragedy. Throughout the year, the Fund provides support where it is needed. Last year, in financial terms, this amounted to a commitment of just over £1m.

It has become a tradition that at Christmas time we provide extra help—perhaps a gift, or more usually, a little more money; all the more welcome to buy presents when children are involved. Once again, though, we need your continuing kindness and generosity to enable us to give this additional seasonal cheer.

At this time last year we received over £73 000—a second record year. Please help once again in the hope that we can make Christmas for those less fortunate than ourselves approach their memory of happier times past.

Contributions marked 'Christmas Appeal' may be sent to the CEO of the RMBF, 24 King's Road, Wimbledon, London SW19 8QN or to the Treasurer of your local guild of this Fund. Thank You.

To those of you who have already contributed—thank you.

$500,000 IARS Frontiers in Anesthesia Research Award—Fourth Recipient

The Board of Trustees of the International Anesthesia Research Society (IARS) announced at the 75th Clinical and Scientific Congress the fourth recipient of the $500,000 IARS Frontiers in Anesthesia Research Award. The award was established by the IARS in 1994 'to foster innovation and creativity by an individual scientist in the field of Anesthesiology'. The fourth recipient is:
Mark A. Schumacher, PhD, MD, University of California, San Francisco, California.

Dr Schumacher's research project is titled 'Stretch-Inactivated Channels in Pain Transduction'. Dr Schumacher is an Assistant Professor in the Department of Anesthesia and Perioperative Care at the School of Medicine, University of California, San Francisco.

British Journal of Anaesthesia/Royal College of Anaesthetists

Smal Project Grants 2001

Monies are available to support specific research projects in anaesthetic departments. Joint applications with basic science departments will be welcome. These grants may be awarded to fund technical staff, research students or post-doctoral research fellows; salaries, or items of equipment. The maximum value of any award will be £20 000, and the *BJA/RCA* will not contribute towards overheads.

The *BJA/RCA* will not be funding either Research Fellowships or Full Project Grants with this round of awards; the aim of these applications is to provide support as 'pump-priming' monies for future more substantive applications.

For further details and forms, please write or e-mail to:

Dr J. W. Sear (BJA Grants Officer), Nuffield Department of Anaesthetics University of Oxford, John Radcliffe Hospital, Headington, Oxford OX3 9DU or john.sear@nda.ox.ac.uk

Closing date for applications is November 30 2001. Late applications will not be considered.

ENT Anaesthesia

London, UK, November 1–2, 2001

A limited number of places are available on a course organized by Dr Ariel Patel and Dr Catrion Ferguson for Institute of Laryngology and Otology, Royal Free and

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EFO® (LORNOXICAM) INJECTION AND TABLETS rescribing information (refer to Summary of Product Characteristics before rescribing). **Presentations:** Xefo 8mg Powder for Injection - 10ml vial containing rnoxicam 8.6mg. Xefo Tablets - Film-coated tablets containing lornoxicam 4mg or mg. **Uses and Dosage:** Moderate post-operative pain (short-term) - Tablets: -16mg daily (maximum single dose 8mg). Injection (iv or im): give in 8mg doses, up o 16mg daily although an additional 8mg dose may be given in first 24 hours. Limit reatment to 2 days. Pain associated with acute lumbo-sciatica - Tablets: -16mg daily (maximum single dose 8mg). Injection (iv or im): 8mg twice daily or 1-2 days. Pain and inflammation in osteoarthritis and rheumatoid arthritis: Tablets: 12mg daily in 2-3 divided doses. Injection and Tablets not indicated for [illegible] 18 [illegible]). Injection not indicated for adults aged 65 years or over. **Contra-indications:** Allergy, hypersensitivity, peptic ulceration, severe renal impairment, pregnancy or lactation. **Warnings and precautions:** Mild-moderate renal impairment, liver disease, coagulation disorders, hypertension or obesity, long term treatment (>3 months), elderly patients. Monitor renal function in patients undergoing major surgery, with stressed renal function, cardiac failure, on diuretics or taking concomitant treatment suspected of causing renal damage. **Undesirable effects:** Frequency 1-10%. Tablets: Abdominal pain, diarrhoea, dizziness, dyspepsia, headache, nausea and vomiting. Injection: Abdominal pain, dizziness, fatigue, headache, injection site reactions, nausea, somnolence. See SPCs for details of adverse reactions occurring with frequency of less than 1%. **Legal categories, marketing authorisation numbers, package quantities and prices:** Xefo 8mg Powder for Injection: POM. PL 18467/0008. 1 vial - £2.25. Xefo 8mg Tablets: POM. PL 18467/0007. 30 tablets - £8.85. Xefo 4mg Tablets: POM PL 18467/0006. 30 tablets - £8.85. **Marketing authorisation holder:** CeNeS Limite Compass House, Vision Park, Chivers Way, Histon, Cambridge CB4 9ZR. Date o preparation: July 2001. **References:** 1. Nørholt SE, *et al. Pain* 1996; **67**: 335-34 2. Ilias W, Jansen M. *Br J Clin Pract* 1996; **50** (4): 197-202. 3. Rosenow D van Krieken F, Stolke D, Kursten FW. *Clin Drug Invest* 1996; **11** (1): 11-1 4. Kidd B, Frenzel W. *J Rheum* 1996; **23** (9): 1605-1611. 5. Comprehensiv evaluation of safety data in patients treated with lornoxicam. Data on file 199 Eagle image © Dorling Kindersley.

XHJA001 July 2001

CeNeS

University College Medical School and Royal National Throat, Nose and Ear Hospital.

For further information,please contact: Joy Gibney or Charmaine Henry, Administration, Institute of Laryngology and Otology, 330-336 Grays Inn Road, London WC1X 8EE, UK. Tel: +44 (0)20 7915 1514/92; Fax:+44 (0)20 7837 9279. E-mail: j.gibney@ucl.ac.uk/c.henry@ucl.ac.uk

5th Annual Conference of the Indian Association of Cardiovascular and Thoracic Anaesthesiologists

Bangalore, India, November 2–4, 2001

It is hoped that there will be a CMF in cardiac anaesthesia on one day preceding the conference, for the benefit of the postgraduate students.

For further information, please contact: Dr Suresh K. Ghaste, Organising Secretary, VIACTA Conference, Professor and Head of Department of Anaesthesiology, Sri Jayadeva Institute of Cardiology, M. H. Complex, Bangalore, S60 002, India. Tel: + 0 6707575 Ex. 138, E-mail: skghaste@yahoo.com

European One Day Course in Spinal Endoscopy

Bradford Royal Infirmary, England, November 9, 2001

This course will be of interest to all those involved with central neural blocks and especially to those involved with the investigation and management of patients with back and radicular pain.

For further information and to secure a place please contact: Dr J. Richardson, MERIT Centre, Bradford Royal Infirmary, Bradford BD9 6RJ, England. Tel: +44 (0) 1274 364271; Fax: +44 (0) 1274 366811

Primary FRCA Revision Course

Leicester Royal Infirmary, Leicester, UK, December 3–5, 2001

An intensive revision course for the Primary FRCA based on small group tutorials and including written and oral examination practice. Fees: £245 (including lunch and refreshments); £270 for two nights residential; £280 for three nights residential (limited availability). Course directors are Dr Justiaan Swanevelder and Dr Jonathan Thompson. Places are strictly limited.

For a booking form, please contact Christine Gethins on +44 (0) 116 258 5291 (anae@le.ac.uk).

International Scientific Meeting to celebrate the retirement of Professor R. S. Jones OBE, after 40 years in Veterinary Anaesthesia

The Racecourse, Chester, UK, December 6–7, 2001

Theme for the first day: 'Forty Years of Veterinary Anaesthesia'.
Theme for the second day: 'One Vet's Multidisciplinary Contributions'.

For further details please contact: Professor J. M. Hunter. Tel: +44 (0)151 706 4008; Fax: +44 (0)151 706 5884; E-mail: jwa@liv.ac.uk

3rd National Conference Indian Society of Neuroanaesthesiology and Critical Care (ISNACC-2002)

Mumbal, India, January 12–13, 2002

For further details contact: Dr (Mrs) Kanchan S. Jagger, Room No. 423, 4th Floor, Department of Anaesthesia, L.T.M. Medical College Sion, Mumbal: 400022, India. Tel: +91 22 4022976 (O), +91 22 4371811 (R); Fax: +91 22 4076100; Email: kanchanjagger@yahoo.co.uk or isnacc2002@sify.com

20th Annual Symposium Clinical Update in Anaesthesiology and Advances in Techniques of Cardiopulmonary Bypass

Paradise Island, Bahamas, January 13–19, 2002

Abstract, Poster and Free Papers Information: (**Deadline – November 1, 2001**) Helen Phillips, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1010, New York, NY 10029-6574, USA. Tel: +1 212 241 7467; Fax: +1 212 426 2009; E-mail: helen.phillips@mssm.edu

Welcome to the second Euro-PNB winter symposium!

Postgraduate Course on Peripheral Nerve Blockade in Surgery and Pain Management for anaesthesiologists
Excelsior Mila Hotel, Crans-Montana, Switzerland, January 16–19, 2002

Meet European experts in this stimulating course with workshops in an exciting environment.

Lecturers: Borgeat, Zürich, CH; J. Büttner, Mumau, DE; X. Capdevila, Montpellier, FRA; A. Ekblom, Stockholm, SE; E. Gaertner, Strasbourg, FRA; S. Gligorijevic, Zürich, CH; M. Jöhr, Luzern, CH; Z. KoscicIniak-Nielsen, Copenhagen, DK; D. Selander, Södertälje, SE; N. Suthcliffe, Glasgow, UK; T. Wildsmith, Dundee, UK.

Full participation certifies 15 Eu CME points. Fee: 250.-CHF. Places are limited to 40 delegates.

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Registration before December 1, 2001 to: Assoc. Prof. Alain Borgeat, Head of Anaesthesia and Intensive Care, Orthopedic University Clinic, Balgrist/Zürich, Forchstrasse 340, CH-8008 Zürich, Switzerland.

Tel: +41 1 386 38 32; Fax: +41 1 386 16 09; E-mail: aborgeat@balgrist.unizh.ch

13th SW Thames Anaesthesia Update

Belle Plagne, French Alps, January 28–February 1, 2002

The scientific programme will include lectures and discussions on: Acute and Chronic Pain; Paediatric Update; Obstetric Anaesthesia; Neurology and Anaesthesia; ITU and Relevant Medical Topics; Cardiothoracic Anaesthesia; Day Case Surgery; Regional Blocks; New Drugs Update; Training and Education; Information Technology; Free Papers. Case Presentation Competition. Guest Speakers, Workshops, Videos on new Drugs, Equipment and Techniques.

Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: December 10, 2001. Meeting approved for CEPD.

For full information and to secure a place please contact: Dr J. B. Liban, Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT. Tel: +44 (0) 208725 0018; Fax: +44 (0) 208725 3135; E-mail: liban@mailbox. co.uk; Website: www.anaesthesiaupdates.com

International Anaesthesia Research Society Annual Clinical and Scientific Congresses

March 16–20, 2002
IARS 76th Clinical and Scientific Congress, San Diego Marriott Hotel & Marina, San Diego, California, USA.

March 22–26, 2003
IARS 77th Clinical and Scientific Congress, New Orleans Marriott, New Orleans, Louisiana, USA.

March 27–31, 2004
IARS 78th Clinical and Scientific Congress, Tampa Marriott Waterside Hotel, Tampa, Florida, USA.

March 11–15, 2005
IARS 79th Clinical and Scientific Congress, Hilton Hawaiian Village, Honolulu, Hawaii, USA.

Contact information: IARS, 2 Summit Park Drive, Suite 140, Cleveland, OH 44131, USA. Tel: +1 216 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Web: www.iars.org

Putting New Flesh on Old Bones: a major conference on Issues in the Perioperative Care of Geriatric Trauma

The Netherwood Hotel, Grange-Over-Sands, UK, May 10, 2002

Speakers include: Nigel Sharrock (New York); Martyn Parker (Peterborough)

Deadline for free paper abstracts: February 1, 2002.

Please contact Dr Andrew Severn for details: Tel: +44 (0)1524 583517; Fax: +44 (0)1524 583519.

Australian and New Zealand College of Anaesthetists Annual Meeting

Brisbane Convention and Exhibition Centre, Brisbane, Australia, May 11–15, 2002

For further information please contact:

ANZCA 2002 Secretariat, PO Box 1280, Milton QLD 4064, Australia.

Tel: +61 (0) 7 3858 5537; Fax: +61 (0) 7 3858 5510; E-mail: anzca2002@im.com.au; Website: www.anzca.edu.au

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Anaesthesia outside the square: CECANZ Conference 2002

Christchurch, New Zealand, September 18–20, 2002

For information, please contact: Conference Secretariat Joy Mehlhopt, Conference Innovators, P.O. Box 1370, Christchurch, New Zealand.

Tel: +61 3 379 0390; Fax: +61 3 379 0460; E-mail: joy@conference.co.nz. Website: www.cecanz2002.org.nz

Société Française d'Anesthésie et de Réanimation

Annual congresses will take place in Palais des Congrés, Porte Maillot, Paris on the following dates:

September 26–29, 2002
September 18–21, 2003
September 20–October 3, 2004
September 29–October 2, 2005

For further information, please contact: SFAR, 74, rue Raynouard, F-75016 Paris, France. Tel: +33 1 45 25 82 25; Fax: +33 1 40 50 35 22; E-mail SFAR@invivo.edu

Dingle 2002—4th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 2–6, 2002

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

Australian Society of Anaesthetists National Scientific Congress

Adelaide, Australia, October 26–30, 2002

This is the Society's premier scientific conference, held in an interesting part of the world.

For further details, please contact: Festival City Conventions, P.O. Box 949, Kent Town, S.A. 5071, Australia. Tel: +61 (0)8 8363 1307; Fax: +61 (0)8 8363 1604: E-mail: asa2002@fccconventions.com.au

8th International Congress of Cardiothoracic and Vascular Anesthesia
19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:
8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H.Rosenberg, Helsinki University Hospital, Helsinki FIN00029 HUS, Finland.

E-mail: per.rosenberg@hus.fi
Or: CONGREX/Blue & White Conferences Oy

E-mail: congrex@congrex.fi
Web address: www.congrex.fi

Dingle 2003—5th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 1–5, 2003

For further information contact:

Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

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1111 Postoperative Renal Dysfunction
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1121 β-Adrenergic Agonists and Liver Blood Flow
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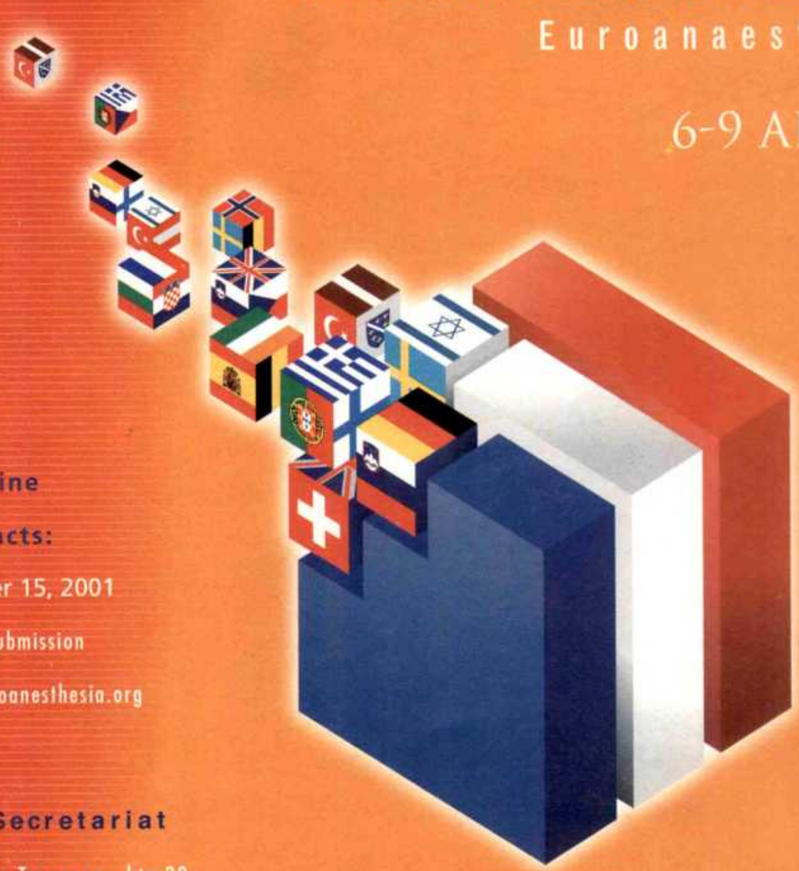

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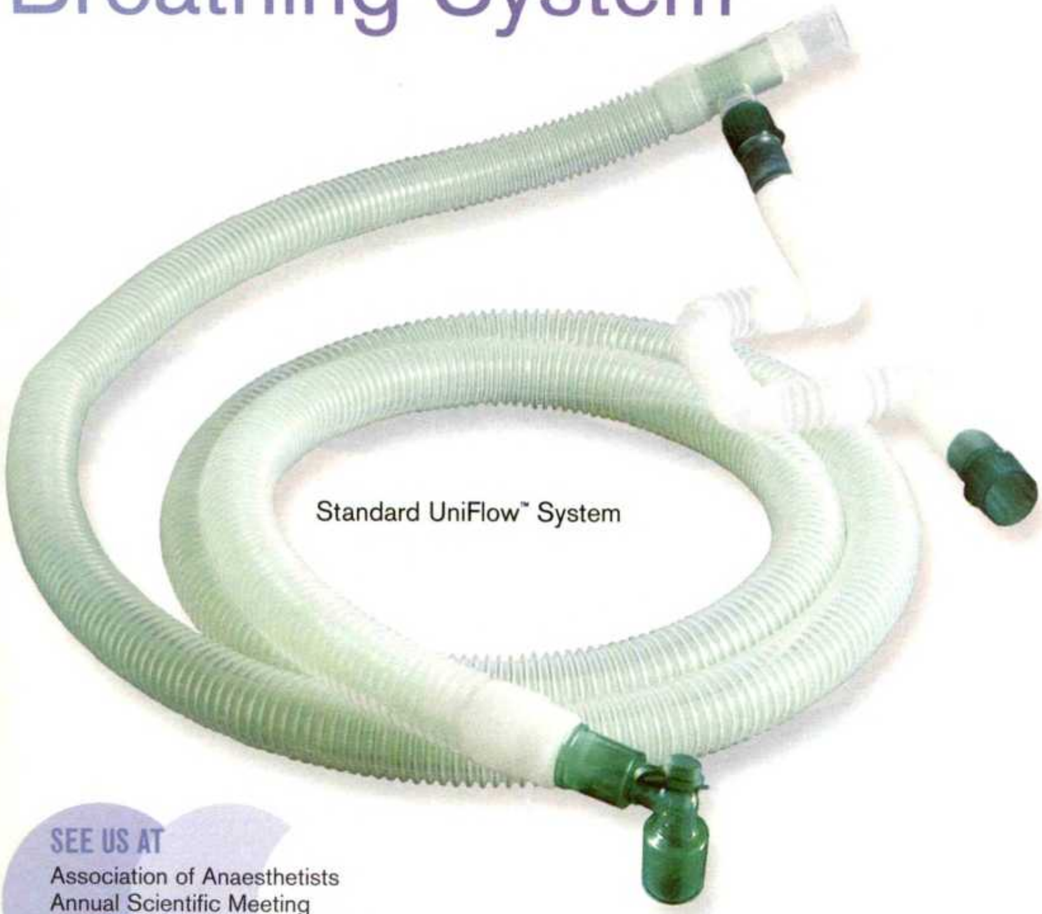

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Editorial I

Dexmedetomidine: a real innovation or more of the same?

Sedation of critically ill patients is one of the commonest interventions in the intensive care unit (ICU). Historically, the purpose of sedation was to allow a patient's ventilation to be controlled and, even today, sedation and ventilation remain inextricably linked. More recently, the comfort aspects of sedation have been emphasized,[1] and we have become more aware of the safety issues involved. Morbidity[2] and mortality[3] have been reported with sedative agents, and even the way sedative agents are given may influence the patient's outcome.[4] Sedation scores and sedation-measuring devices[5] are used in an attempt to reduce the risks of over-sedation, particularly excess drug administration and drug withdrawal reactions. Sedation has become safer and developments in ventilators and airway maintenance have made deep levels of sedation less necessary. In spite of this, problems related to sedation are common in the ICU and are often difficult to deal with.

One response to sedation-related problems has been to demand new and, hopefully, better sedative agents. Usually, when a new agent is introduced, there is initially enthusiasm for its use. When the first serious side-effects are reported, this enthusiasm wanes and may be replaced by cynicism. Finally, the agent finds its place in the armamentarium of each individual practitioner. Sedative agents have been introduced into the ICU and this pattern of response has happened. Our present range of sedative agents is limited but individual agents have found their place in the intensive care pharmacopoeia; nevertheless, the underlying problems of sedation remain. Now we have dexmedetomidine. This selective α_2 adrenoreceptor agonist is already licensed in the USA for short-term postoperative sedation. It is the active ingredient of medetomidine, which has been used as a veterinary anaesthetic for some time [6].

α_2 Adrenoreceptors are found in the central and peripheral nervous systems and in autonomic ganglia at both pre- and post-synaptic sites. Stimulation of pre-synaptic receptors in sympathetic nerve endings inhibits release of norepinephrine, while central post-synaptic receptor stimulation inhibits sympathetic activity; both effects result in a decrease in blood pressure and heart rate and an increase in sedation. Stimulation of α_2 adrenoreceptors in the spinal cord produces analgesia. After administration, dexmedetomidine is distributed rapidly; it undergoes extensive metabolism in the liver and excretion in both urine and faeces.[7]

The experience of dexmedetomidine suggests that it provides adequate short-term sedation for patients requiring intensive care.[7] Although it reduces the stress response to surgery,[8] it does not interfere with steroid formation in the way that etomidate does.[9] It provides analgesia and reduces opioid requirements,[7] but does not affect respiratory rate or carbon dioxide clearance; in fact, it may improve oxygenation.[10] The major problem with dexmedetomidine may be its haemodynamic effects. Hypotension and bradycardia have been reported, particularly with more rapid infusion and in patients with pre-existing cardiac problems.[7] [11] The study reported by Venn and Grounds in this issue[12] compares dexmedetomidine with propofol in patients requiring short-term post-operative sedation. The two agents provide comparable sedation acceptable to clinicians and patients, dexmedetomidine reducing analgesic requirement and heart rate.

One of the fascinating differences with dexmedetomidine is the quality of sedation it produces. Because it has a different mode of action, patients experience sedation in a different way.[13] Drugs acting on the GABA system, such as midazolam and propofol, produce a clouding of consciousness which is viewed as a part of the spectrum between consciousness and anaesthesia. Dexmedetomidine, acting on α_2 adrenoreceptors, sedates patients by reducing sympathetic activity and the level of arousal. Thus, patients lie calmly in bed but are easily roused to full consciousness. Sedation with GABA-related agents can cause paradoxical agitation[14] as well as tolerance, dependence and even addiction,[15] which are probably related to changes in the receptors with long-term drug administration. These phenomena have not been described with dexmedetomidine, but its use has been confined to short-term sedation. It will be interesting to study the longer-term effects of dexmedetomidine administration.

What changes might dexmedetomidine bring to sedative practice? Should we use it in the same way as more conventional agents or can we use it differently? Continuous infusions and intermittent bolus doses given by nursing staff are the current methods of sedative administration. Is this a drug that can be given by a

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patient-controlled system? Does this different type of sedation require a different monitor? Sedation scores have been devised in response to GABA-mediated drugs and opioids; sedation monitors have been developed to assess the depth of anaesthesia. Should we use the same criteria and methods that we currently use to monitor sedative level with dexmedetomidine? In the study by Venn and Grounds[12] they used the conventional Ramsay scale and bispectral index and found no difference between propofol and dexmedetomidine. Does this do justice to the sedation produced by dexmedetomidine?

We have strategies and protocols for dealing with withdrawal from benzodiazepines and opioids when they occur in critically ill patients.[15] Withdrawal from clonidine is associated with rebound hypertension.[16] This has not yet been studied with dexmedetomidine. We now know a lot about the safety of individual sedative agents and a little about their safe use in the critically ill. We need to know a lot more about dexmedetomidine before we can use it with confidence.

Fundamentally, whether or not dexmedetomidine turns out to be just another sedative agent depends on how we use both the drug and the opportunity it provides. If we use this drug in the same way as our existing agents, it may well turn out to be just another sedative agent and we will become cynical as the side-effects are reported. However, if we use this different agent in a different way, we have the chance to reconsider what we want from sedation and possibly to take the sedation of critically ill patients to a new level. This is a real opportunity. An opportunity not only to try out another drug but also to re-evaluate sedation in the critically ill.

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Editorial II

Monitoring medical devices: the need for new evaluation methodology

The publication of the document entitled 'An organisation with a memory: report of an expert group on learning from adverse events in the NHS chaired by the Chief Medical Officer'[1] by the Department of Health (DoH) last year has focused attention on preventable failures in NHS care. It was observed that the mechanisms for detecting, reporting and analysing failures were incomplete and frequently flawed. Following on from this, it was noted that, in cases where important lessons were learned, there was often a failure to embed these into future practice, resulting in repetition of the same failures. The National Patient Safety Agency[2] has recently been created to address these issues.

The observations made in the DoH document are particularly true in the areas of perioperative medicine and critical care, where several factors predispose to failure of care. These factors include the proliferation of high-technology medical devices;[3] the low signal provided by individual devices in the context of the noise represented by clinical and other technological data inputs;[4–6] the complex and demanding nature of clinical workloads; and human factors[7] acting at the individual, team and organizational levels. Individuals are often expected to master the use of a large number of complex medical devices, which makes great demands on memory, recognition and decision-making. Failure of care in the context of medical device usage is a substantial problem. Over 6600 adverse incidents involving medical devices were reported to the Medical Devices Agency in 1999, including 87 deaths and 345 serious injuries.[1] Mishaps in this context are frequently categorized as 'human error' or 'equipment malfunction'.[8] However, there seems to be limited appreciation of the extent to which interactions between medical devices and their human operators affect safety.

This deficiency may prevent the correct categorization of medical mishaps, but it also has a more strategic significance, as it prevents the appropriate application of systems methodology in the analysis of failures (as recommended by the DoH). Such analyses identify mishaps that are related to device usability and they also provide the basis for improving device–operator interfaces, and thus help reduce the frequency of such mishaps. In this context (and in this discussion), the term 'usability' refers to the quality of a device's user interface. It encompasses factors such as ease of learning, error prevention, help and documentation, physical controls, the perception of auditory and visual signals, the style and efficiency of the interaction, and the cognitive load placed on the user. This represents an important but under-investigated area, attention to which may improve patient safety substantially.

Detecting failures attributable to poor usability

Superficially, the detection and categorization of mishaps would appear to be a straightforward process. Failure of care is traditionally described in terms of unexpected patient morbidity and mortality and near misses. However, less obvious end-points that may be affected by suboptimal usability include a decreased margin of patient safety, decreased organizational productivity and staff morbidity, such as stress and low morale. These end-points are more difficult to quantify and may go undetected. A further detection problem arises from the traditional dichotomy between human error and equipment malfunction. The interaction between a medical device and its user can be a source of problems, and failures can occur in the presence of functionally operational equipment and 'reasonable' users. As there is poor appreciation of this class of problem, the detection rate is likely to be low. It is likely that a proportion of these events could be avoided by the availability of improved user interfaces.

Difficulties in reporting and analysing usability problems

Reporting methods in place that are capable of highlighting problems with medical devices include critical incident reports, morbidity and mortality surveillance, reports to the Medical Devices Agency, national audits such as the National Confidential Enquiry into Perioperative Deaths, and clinical litigation settlements. In any voluntary reporting system, an individual is less likely to self-report if they are likely to focus attention on their own presumed inadequacies. This is likely to continue to happen if the focus remains on human error.

The existing limitations in detecting and reporting interaction problems with medical devices flow on to the analysis phase. Again, limited understanding of the interaction between humans and devices and its importance will lead to shortcomings in analysing the available information. Even if there were a good understanding of the interaction process, there is no widely accepted method for analysing and subsequently communicating medical device usability problems. The DoH document also makes the point that there is no reliable mechanism for analysing information collected through different reporting channels to distil common themes or lessons.

Implications for active learning

The DoH describes active learning as a process in which lessons learned from failure are embedded in an organization's culture and practices. In the context of a discussion about medical devices, this notion can be extended in a number of ways. Strategies to close the learning loop should include the development of manufacturing standards for medical devices which incorporate both functional and usability specifications Deficiencies in usability design also need to be fed back to manufacturers to allow ongoing improvement Individuals responsible for procuring medical devices for the NHS should have access to device evaluations which quantify usability, allowing them to choose the safest equipment. However, this information is not easily available, and recently published equipment evaluations have given this area a limited and qualitative treatment.[9 10]

Strategic approaches to usability analysis: problems and potential solutions

At present, significant barriers prevent progress. The first problem is the absence of standardized usability evaluation methods for medical devices. Secondly, there is no widely recognized protocol for describing and communicating such usability problems.

Over the last few decades, a significant number of usability evaluation methods have been developed by the computer industry for assessing the human–computer interface. Preece and colleagues[11] provide a categorization of these methods, which include usage data analysis, experimental evaluation and benchmarking, interpretive evaluation and predictive evaluation. 'Usage data analysis' involves the collection of usage data (observation of users directly or with video cameras), software logging (recording and analysis of user keystroke chains) and the collection of user's opinions. 'Experimental evaluation' uses traditional hypothesis-testing with varying degrees of scientific rigour, while 'benchmarking' is widely used for comparing computer hardware performance with a reference point. In 'interpretive evaluation', evaluators immerse themselves in the domain of the user in order to understand the user's requirements and problems with existing systems. It is principally a product development tool. 'Predictive evaluation' attempts to predict the usability problems that a computer system will exhibit. An example from this last group is 'heuristic analysis', in which the evaluator employs a checklist to detect the presence of desirable or essential usability features and the absence of known usability problems.

Whilst some of these evaluation techniques are clearly only relevant to product developers, others may have significant promise in evaluating and comparing existing medical devices. Collecting users' opinions and heuristic analysis are the only usability evaluation techniques in common use for the after-market assessment of devices. A major drawback of these methods is that they are qualitative and provide limited information. Examples of quantitative measurements that may prove useful include the following:

- Time taken to achieve a given speed of task completion (as a measure of ease of learning)
- Decrement in error rate over time (as a measure ease of learning)
- Number of keystrokes or other actions required to achieve a particular goal
- Time taken to achieve a particular goal
- Number of cognitive tasks (such as recollections, recognitions and decisions) required to achieve a particular goal (allowing inferences to be made about the likelihood of human error) ,
- Performance decrement after a period of absence (as a measure of memory loading).

These techniques fall into the categories of usage data analysis, experimental evaluation and benchmarking, and predictive evaluation. Such measurements may demonstrate significant differences between devices from competing manufacturers. Some of these methods may have significant promise in the medical devices domain, but further work is needed to evaluate, adapt and validate the most relevant techniques.

Implications for equipment design

Human error is a frequently cited cause of medical mishaps. Inadequacies in training, experience and supervision are often identified as preventable factors contributing to human failure.[12] The fact remains that humans will always be susceptible to error.[13] Without diminishing individual or corporate responsibility, it is important to consider ways in which monitoring equipment can be engineered and designed in order to prevent human error. In the context of perioperative medicine and critical care, it should also be remembered that operators of medical equipment work in a difficult environment, often with numerous complex devices, and are frequently subject to factors such as stress, fatigue and fluctuating workloads. These factors further impair the cognitive processing necessary to operate medical devices, and should be factored into the design. The approach to these problems falls within the domain of equipment usability design rather than the functional specification of equipment. Undoubtedly, many manufacturers have made significant progress in improving the user interfaces of their devices. These gains have been offset to some extent by the diversity of approaches to interface design, which reduces the extent to which users can transfer their existing knowledge to different devices. Furthermore, the diversity of interface design has been implicated in failures of care.[14]

We welcome recent developments aimed at addressing medical device safety, including the creation of a Committee on Safety of Devices.[15] However, the specific issue of technology in perioperative medicine and intensive care and the improvement of human–device interfaces in this setting may require more focused attention. There is a clear need to recognize the contribution of device usability to good clinical care. We need to evolve standardized approaches for the evaluation of medical device usability and to provide means by which such standardized evaluations can be disseminated to the NHS community at large, so as to avoid the need for expensive re-evaluation by individual user groups. Such standardized evaluations would also facilitate the comparison of competing devices and contribute to rational procurement and purchasing strategies.

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Editorial III

Pain relief after thoracotomy

In Genesis, it states that the Lord caused a deep sleep to fall upon Adam so that his rib could be removed to create the female of the species.[1] It would, in the current healthcare climate, be interesting to look at outcome studies in both species! It would also seem that it was prophesied that thoracic surgery would be very painful and would require appropriate and effective treatment.

Most anaesthetists would agree that there is considerable pain after thoracotomy and that excellent analgesia is required. However, the ideal method has yet to be developed. What, therefore, are the advantages and disadvantages of current regimens and what does the future hold?

Worldwide, morphine is probably the most commonly used drug despite its well-known disadvantages. However, to be effective, it is recommended that regular doses are given at regular intervals.[2] The former is probably attainable while the latter is probably not. In the 1960s and 1970s this approach was used by the majority of anaesthetists. The major problems were that patients were either in pain or asleep and were unable to expectorate secretions from the respiratory tract. Inevitably, a high percentage of these patients returned to the operating theatre for a bronchoscopy to remove retained secretions. Some of these patients developed pneumonia and occasionally died.

It was, therefore, reasoned that the way to achieve the best analgesia was to try to obtain an appropriate and constant blood level of an analgesic agent. Thus, constant i.v. infusions became, and indeed still remain, popular.[3 4] These techniques, however, were potentially unreliable because of the apparatus involved in the drug delivery. There was also a concern that any additional top-ups, if and when required, could lead to overdosage and in particular, respiratory depression. Such concerns helped in the development of high dependency units.

The next development was patient controlled analgesia (PCA)[5]. Although this system worked well, when sleep occurred, drug delivery stopped. The patient subsequently awoke in pain and had difficulty in coughing so that the secretions that had accumulated during the sleep period were not expelled from the respiratory tract.

Therefore, it seemed that the ideal approach might be a background infusion with PCA back up. Such a regimen could produce excellent pain relief despite the possible disadvantages. There is, however, some evidence whereby the patient, usually the more elderly, became confused because of a combination of the drug effects and loss of the natural circadian rhythm. This confusion prevented co-operation with the physiotherapist; sputum retention and occasionally pneumonia ensued.

The increased interest in epidural analgesia in the 1980s, particularly in obstetrics, provided the anaesthetist with an ideal opportunity for dealing with thoracic pain though with an equal potential for disaster in the form of spinal cord damage.[6] The development of this method led to robust international debates which revolved around several issues.[7–11]

- Should the epidural catheter be inserted while the patient is awake or asleep?
- Should the epidural be placed in the thoracic or lumbar region?

Table 1 A recommended solution for epidural use

Fentanyl 10 ml, 0.5% bupivacaine 10 ml, saline 20 ml	Total volume 40 ml
Fentanyl concentration	12.5 $\mu g\ ml^{-1}$
Bupivacaine concentration	0.125%
Epidural infusion rate	0.05–0.10 $ml\ kg^{-1}\ h^{-1}$

- Should the technique be loss of resistance to air or saline?
- Should the drug used be either a local analgesic agent, an opioid, or a mixture of both?[12]
- Where should the patient be looked after in the post-operative period—in a HDU/ICU or on a general ward?

There is still no universal agreement but a general theme is beginning to emerge. Many anaesthetists believe that awake insertion is the safest approach as the patient will let the operator know if the needle approaches and touches the dura. There is some evidence that this is not necessarily so and that complications do still arise.[13, 14]

The exact level of placement is in dispute though it is natural to think that a drug works best at the area required. There are those who advocate that the tip of the epidural catheter should be sited around T4–T6. When placed in this area, fat-soluble analgesic drugs should be used as they diffuse into the correct segmental area. There are those, however, who prefer to use the lumbar route and thread the epidural catheter cephalad for several centimetres. It would appear in these situations that there is a preference for water-soluble, opioid drugs.

There has been an increasing tendency to use loss of resistance to saline and not air because of the possibility of causing an air embolism. The difficulty is deciding, particularly under sterile operating conditions, whether the liquid coming back from the Tuohy needle is either saline or cerebrospinal fluid. The differentiation is extremely important as it will have considerable bearing on the subsequent injection and actions of the preferred drugs.

There has also been considerable debate concerning the drugs used. On the one hand, local analgesic solutions can lead to a drop in peripheral vascular resistance as a result of sympathetic block. The danger that follows is that an increased fluid load is given intravenously. Occasionally, if excessive fluid is administered particularly after right pneumonectomy, the pulmonary artery pressure rises and pulmonary oedema can ensue.[15, 16] This has a poor prognosis. On the other hand, when using opioids, there is a danger that there may be patchy analgesia, which requires some form of back up for break through pain. Overdose is, therefore, a possibility. Consequently, a mixture of both is gaining in popularity, for example fentanyl 12.5 $\mu g\ ml^{-1}$ and 0.125% bupivacaine in saline (Table 1).

However, there remains a major problem in UK practice; what to do when faced with, for example, bronchoscopy and possibly proceed to thoracotomy? All anaesthetists would agree that inserting an epidural for what might turn out to be a bronchoscopy would be entirely inappropriate. The next question is, therefore, what to do if the decision is made to proceed?

There are colleagues who recommend that an epidural should be inserted with the patient asleep. After all, similar techniques using local analgesia have been, and continue to be, used in neonates, infants and children where the potential for harm is probably greater and for a longer period of time. Others would argue that the safest method would be to use the lumbar route to avoid possible spinal cord damage. However, a recent editorial has suggested that the anatomy of the lower end of the spinal cord is not constant and that such an assumption may produce a false sense of security.[13] Furthermore, another recent study has shown that many anaesthetists cannot accurately identify the interlumbar vertebral spaces.[17]

Richardson, by contrast, has argued that there is no need to insert an epidural needle, as a catheter appropriately placed beneath the parietal pleura is equally effective.[18, 19] In his hands, this technique has produced excellent results. However, this technique is not widely used as both surgical and anaesthetic expertise are required to accurately place the catheter and to manage the therapeutic regimen thereafter. There are also other problems, such as hypotension, and for example in the original paper, 10% of patients needed i.v. opioids to cover the break-through pain. In the event of failure of either system, the final fall back would probably be a constant infusion with superimposed PCA. In children, nurse controlled analgesia (NCA) may also be an option.

However, even when these methods are used, there still remains the problem of movement and referred pain, particularly to the shoulder. The use of NSAIDs, either orally or rectally, has become popular and follows on from the original work by Kennan and colleagues and Appadurai and colleagues which showed that similar drugs were good at counteracting movement pain.[20, 21] Shoulder pain can also be treated by infiltrating the fat pad around the phrenic nerve with 1% lidocaine at the level of the diaphragm after lung resection. It may be that if a long-acting drug such as bupivacaine is used in greater volumes, results could well improve further.

There are, of course, other methods such as cryotherapy,[7] constant pleural infusion and the use of regular paravertebral blocks. These methods, however, do not seem popular.

In the early days when using both thoracic and lumbar epidurals for the relief of pain, it was felt that the patient should be nursed postoperatively in either an ICU or HDU. Currently, it would seem that most thoracic units have a HDU for these patients. The question of nursing these patients outside such areas has both advocates and opponents, and could well be a subject of a future editorial particularly when risk management issues are considered.

What therefore does the future hold? There is coming into clinical use a very long-acting preparation based on bupivacaine. In early experiments in man, where the preparation was placed around the appropriate nerves, analgesia lasted for several days. This has great potential in thoracic anaesthesia and other major surgery and will, no doubt, be investigated in the future.[22]

Ideally, it seems that any regimen used should be able to treat both wound and movement pain, prevent mental confusion and enable the patient to breath deeply and expectorate. Currently, I believe that an epidural solution using a combination of fentanyl 12.5 $\mu g\ ml^{-1}$ and 0.125% bupivacaine with either oral or rectal NSAIDs is the most effective. The infiltration of the appropriate phrenic nerve can give an additional dimension.

Sadly, the best regimen will never be agreed because each patient and anaesthetist are different. A double blind clinical trial will be extremely difficult, if not impossible, to conduct. In addition, it would be very difficult to obtain the necessary ethical permission. It may, therefore, be that the answer may evolve from evidence-based anaesthesia. This will undoubtedly include patient choice, informed consent, risk assessment and outcome studies to mention but a few issues.

Finally, it may be prudent to reflect on a lesson learned many years ago from J. Alfred Lee: 'There is nothing wrong with anaesthesia, it is the anaesthetists that are at fault'. Hence, the current philosophy of knowledge, skills, attitudes, and appropriate research will most certainly be a step in the right direction holding the promise of excellent analgesia for patients who have had major thoracic and other surgical procedures.

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CLINICAL INVESTIGATIONS

Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions[†]

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The α_2 agonist dexmedetomidine is a new sedative and analgesic agent which is licensed in the USA for post-operative intensive care sedation. We compared dexmedetomidine with propofol in patients requiring sedation in intensive care. Twenty adult patients expected to require a minimum of 8 h artificial ventilation after surgery were randomized to receive sedation with either dexmedetomidine or propofol infusions. Additional analgesia, if required, was provided by an alfentanil infusion. Depth of sedation was monitored using both the Ramsay sedation score (RSS) and the bispectral index (BIS). Cardiovascular, respiratory, biochemical and haematological data were obtained. Patients' perceptions of their intensive care stay were assessed using the Hewitt questionnaire. Sedation was equivalent in the two groups [median (interquartile range): RSS, propofol group 5 (4–5), dexmedetomidine group 5 (4–6) (P=0.68); BIS, propofol group 53 (41–64), dexmedetomidine group 46 (36–58); P=0.32], but the propofol group received three times more alfentanil compared with patients sedated with dexmedetomidine [2.5 (2.2–2.9) mg h^{-1} versus 0.8 (0.65–1.2) mg h^{-1} (P=0.004)]. No differences were found in arterial pressures between the groups, but heart rate was significantly lower in the dexmedetomidine group [mean (SD) 75 (6) vs 90 (4) beats min^{-1}]. Extubation times were similar and rapid with the use of both sedative agents [median (range) 28 (20–50) and 29 (15–50) min (P=0.63) respectively for the propofol and dexmedetomidine groups]. No adverse events related to the sedative infusions occurred in either group. Despite ventilation and intubation, patients sedated with dexmedetomidine could be easily roused to cooperate with procedures (e.g. physiotherapy, radiology) without showing irritation. From the clinician's and patient's perspectives, dexmedetomidine is a safe and acceptable sedative agent for those requiring intensive care. The rate pressure product is reduced in patients receiving dexmedetomidine, which may protect against myocardial ischaemia. Dexmedetomidine reduces the requirement for opioid analgesia.

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Inadequate sedative techniques may adversely affect morbidity and even mortality in the intensive care unit (ICU),[1 2] and the search for the ideal sedative agent continues. The ideal agent should satisfy the physician's desire for an effective, safe, titratable, cheap and rapidly acting drug that has both sedative and analgesic properties, and should also prevent anxieties and unpleasant memories for the patient. The published accounts of patients' recollections of the ICU are on the whole reassuring,[3–5] but adverse experiences,

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[†] This article is accompanied by Editorial I.

[‡] Dr R. M. Grounds has performed consultancy work on behalf of Abbott Laboratories. Abbott Laboratories have also contributed towards the St George's Hospital Special Trustees research fund, which supports the salaries of research fellows in the ICU

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Table 1 Patient and operative characteristics. median (IQR) or number

	Dexmedetomidine	Propofol
Age (yr)	65 (60–77)	67 (64–74)
Intraoperative fentanyl (μg)	725 (575–1000)	800 (700–1000)
Operation time (h)	5.5 (4–9.5)	4.5 (4–7.5)
APACHE II score	18 (12–19)	16.5 (12.5–20)
Weight (kg)	70 (70–75)	80 (73–83)
Duration of sedative infusion in ICU (h)	10 (8–15)	12 (9–15)
Death	2	1

such as physical discomfort from procedures, inability to communicate and lack of sleep, continue to feature prominently. Thus, when a new sedative agent is compared with the currently used sedative drugs in the ICU, its pharmacokinetic and pharmacodynamic properties will, of course, be contrasted. More importantly, both the physician's and the patient's perceptions of its efficacy require investigation.

The α_2 agonist dexmedetomidine is a new sedative and analgesic agent which has been licensed recently in the USA as ICU sedation for up to 24 h after surgery. Dexmedetomidine provides haemodynamic stability[6] and appears to have no clinically important adverse effects on respiration.[7] Its sedative properties are unique in that it produces only mild cognitive impairment,[8] allowing easy communication between health-care provider and patient in the ICU.[6] We therefore compared the sedative and analgesic properties, safety profile, cardiovascular responses, ventilation and extubation characteristics, and patient perceptions of dexmedetomidine with those of the commonly used i.v. sedative agent propofol in the ICU.

Methods

The St George's Hospital research ethics committee approved the study (Ref. No. 98.06.8) and written informed consent was obtained from all patients. Twenty adult patients (18 yr or older) were investigated. Patients were studied if it was expected that they would require a minimum of 8 h artificial ventilation after complex major abdominal or pelvic surgery. The anaesthetic technique was decided by the individual anaesthetist, although intraoperative analgesia was provided by fentanyl alone, and the dose was recorded. On arrival in the ICU, patients were allocated randomly, using sealed envelopes, to receive i.v. infusions of either dexmedetomidine or propofol whilst being mechanically ventilated, together with the short-acting opioid alfentanil by continuous infusion, for analgesia if required. Alfentanil was used in preference to morphine because recovery after infusion is generally rapid and excretion of active metabolites is not a problem with alfentanil. An initial loading dose infusion of dexmedetomidine or propofol was given to rapidly achieve a steady-state plasma concentration. The loading dose infusion of dexmedetomidine was 2.5 μg kg^{-1} h^{-1} over 10 min followed by a maintenance infusion of 0.2–2.5 μg kg^{-1} h^{-1} into a peripheral or central vein. Propofol was given undiluted as an infusion of 1–3 mg kg^{-1} h^{-1}, after a loading dose infusion of up to 1 mg kg^{-1} over 10 min, if required (Diprivan 1% datasheet). Alfentanil was infused at 0.25–1.0 μg kg^{-1} min^{-1} if the patient indicated he or she was in pain (Rapifen datasheet). The degree of sedation was measured and recorded hourly using the Ramsay sedation score (RSS)[9] and continuously using the bispectral index (BI),[10] and patients were maintained at RSS>2 by adjustments to the sedative regimen. No other sedative or analgesic agents were given, and no patient received spinal or epidural analgesia in the perioperative period.

Patients were ventilated mechanically with oxygen-enriched air to attain acceptable blood gases. The sedative infusion was discontinued, in preparation for extubation, when there was no evidence of bleeding and the patient was alert, cardiovascularly stable, normothermic, and with an arterial oxygen tension ⩾10 kPa on an inspired oxygen concentration <40% and had positive end-expiratory pressure <5 cm H_2O. Once spontaneous respiration had been established with pressure support <10 cm H_2O, a tidal volume of >6 ml kg^{-1}, and respiratory rate ⩾10 breaths min^{-1} but <20 breaths min^{-1}, extubation was undertaken.[11] Extubation time was defined as the time from cessation of sedation infusion to extubation. Heart rate, arterial pressure, central venous pressure and oxygen saturation were monitored continuously. Venous samples were taken for routine haematological (full blood count, coagulation profile) and biochemical (electrolytes, urea, creatinine, liver function, phosphate and calcium) profiles immediately on arrival in the ICU, and then at 24 and 48 h. Cardiovascular and respiratory adverse events were defined as a change in arterial pressure of ⩾40% from baseline, bradycardia <50 beats min^{-1}, tachyarrhythmia, and a respiratory rate <8 or >25 breaths min^{-1} after extubation. Patients were given a Hewitt questionnaire[3] to complete (see Appendix) 48–72 h after discharge from the ICU. The effects of dexmedetomidine on adrenocortical function and endocrine and inflammatory responses were also studied, the results of which are presented separately.[12]

From previous work,[6 7] a sample size of 20 was expected to have a power of 80% to detect a 50% reduction in analgesic requirements and a 20% reduction in heart rate at a significance level of 5%. Data are shown as mean (SD) values unless otherwise stated, and comparisons were made using the unpaired *t*-test. Medians and interquartile ranges (IQR) are quoted for skewed data, and comparisons were made using the Mann–Whitney *U*-test. Haematological and biochemical values and haemodynamics were compared using ANOVA for repeated measures followed by *post hoc* Bonferroni testing. Values of RSS and BI are shown as median (IQR) and were compared by a two-stage method that used summary measures;[13] the area under the curve was calculated for each patient and between-group comparisons were made using the Mann–Whitney *U*-test. $P<0.05$ was accepted as significant. All analysis was carried out using

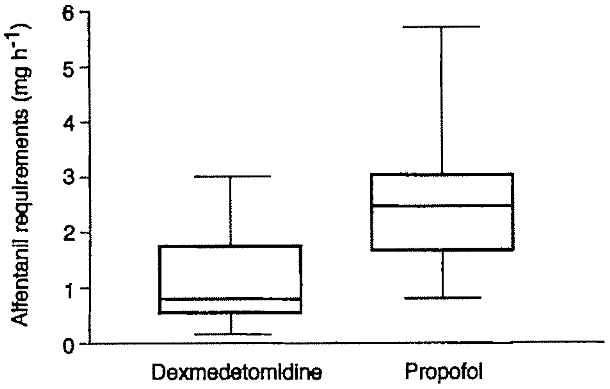

Fig 1 Alfentanil requirements for patients receiving dexmedetomidine and propofol whilst mechanically ventilated in the ICU. Median, IQR and extremes are shown The requirements were significantly lower in the dexmedetomidine group (P=0 004).

the Statview for Windows software package (version 4.57; Abacus Concepts, Berkeley, CA, USA).

Results

There were no statistically significant differences between the two patient groups with respect to age, intraoperative fentanyl requirements, operation time, APACHE II score, weight, duration of sedative infusion and mortality (Table 1). Two patients in the dexmedetomidine group and three patients in the propofol group received sedation for only 6 h because extubation was indicated clinically. Four patients in the dexmedetomidine group and five in the propofol group received sedation for $\geq$12 h. The median (range) dexmedetomidine infusion rate was 0.86 (0.45–1.06) μg kg^{-1} h^{-1}.

Sedation

Over the whole study period, the median (IQR) RSS was 5 (4–5) and 5 (4–6) (P=0.68) for the propofol and dexmedetomidine groups respectively, and BI was 53 (41–64) and 46 (36–58) (P=0.32). The percentage of time spent at what many would consider an ideal depth of sedation (i.e. RSS 2–4) was similar: 49.1% (43.7) for the propofol group and 46.3% (33.1) for the dexmedetomidine group.

Analgesia

Intraoperative analgesia was equivalent in the two groups (Table 1). Patients receiving propofol infusions required significantly more alfentanil [2.5 (2.2–2.9) mg h^{-1}] than patients receiving dexmedetomidine [0.8 (0.65–1.2) mg h^{-1}] (P=0.004) (Fig. 1).

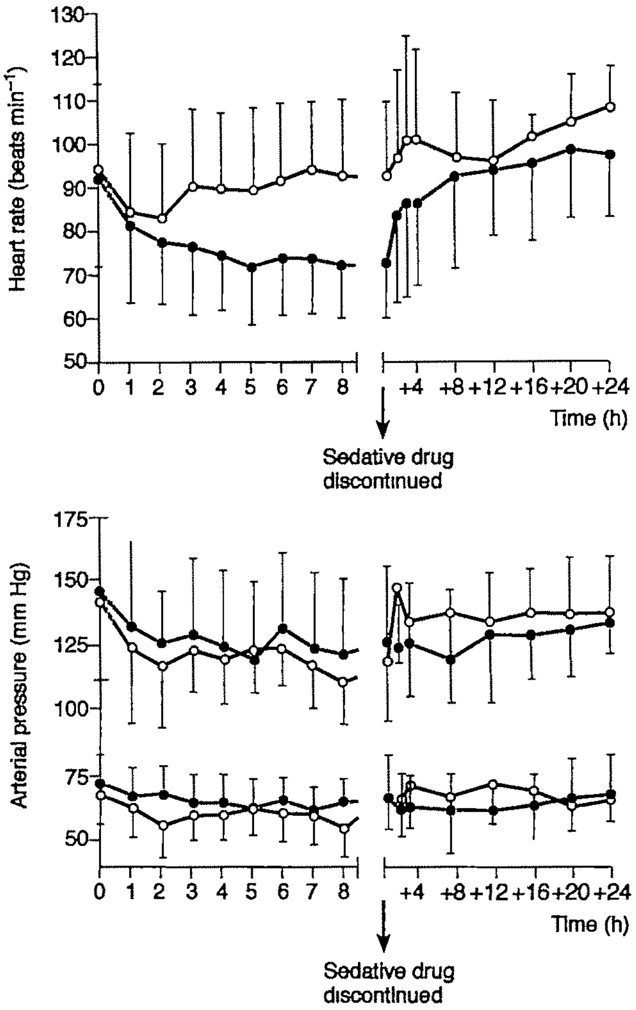

Fig 2 Mean (SD) heart rate (beats min^{-1}) and systolic and diastolic arterial blood pressures (mm Hg) in the dexmedetomidine (closed circles) and propofol (open circles) groups for the first 8 h of intubation and after sedative drug discontinuation. The heart rates were significantly lower in the dexmedetomidine group during intubation (P=0.034 and 0 15 during and after sedative infusion respectively) There were no differences in systolic and diastolic blood pressures between the two groups (P=0 60 during and after sedative infusion). n=10 in both groups except at 7 and 8 h whilst intubated, when n=8 and n=7 in the dexmedetomidine and propofol groups respectively.

Haemodynamics

Patients receiving dexmedetomidine had significantly lower heart rates compared with the propofol group (P=0.034). Arterial and central venous pressures in the two groups were similar at baseline and over the study period (P=0.60 and 0.21 respectively) (Figs 2 and 3). No patient required inotropes, and there were no adverse cardiovascular events in either group. No patient receiving dexmedetomidine exhibited a hypertensive or hypotensive response to the loading infusion dose.

After discontinuation of sedation, heart rates were initially lower in patients receiving dexmedetomidine, but after a return to baseline in these patients there were no differences between the groups (P=0.15). There were no

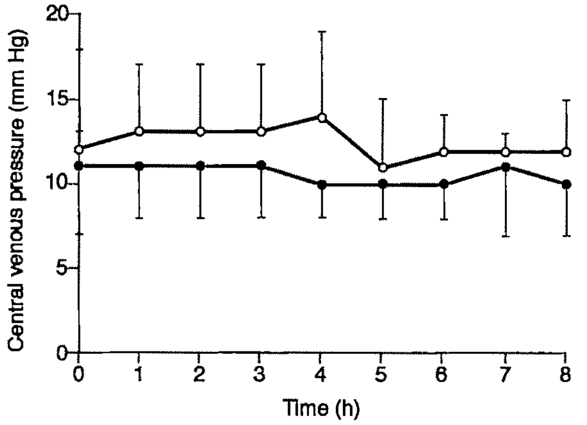

Fig 3 Mean (SD) central venous pressure (mm Hg) in the dexmedetomidine (closed circles) and propofol (open circles) groups for the first 8 h of intubation. There were no significant differences between the two variables at any time point (P=0.21). n=10 in both groups except at 7 and 8 h, when n=8 and n=7 in the dexmedetomidine and propofol groups respectively

differences in arterial pressures between the groups for this period (P=0.60) and no rebound phenomena were seen (Fig. 2).

Ventilation and extubation

Mechanical ventilation variables and arterial blood gas analysis were similar in the two groups for the first 8 h of intubation and artificial ventilation (Table 2). Significant differences existed in the arterial/inspired oxygen ratio between the two groups at baseline and throughout the study (P=0.003). Mean (range) extubation times were 28 (20–50) and 29 (15–50) min respectively for the propofol and dexmedetomidine groups (P=0.63). There were no respiratory adverse events after extubation in either group, and no patient required re-intubation.

Haematology and biochemistry

Analysis of routinely measured haematological and biochemical variables showed no differences between the groups over the 48 h measurement period (Table 3).

There were within-group differences for sodium, urea and creatinine in the dexmedetomidine group, the leucocyte count in the propofol group and the platelet count in both groups.

Median (IQR) urine output for the study period was 141 (104–177) ml h^{-1} for the dexmedetomidine group and 94 (64–146) ml h^{-1} for the propofol group (P=0.12).

Mortality

Two patients died in the dexmedetomidine group and one in the propofol group, on days 14, 17 and 35 respectively, after initially recovering well.

Patient experiences (Table 4)

Memory of ICU experiences

The majority of patients receiving dexmedetomidine recorded the length of stay in the ICU accurately, in contrast to those in the propofol group (P=0.023). However, only a few patients in both groups remembered the duration of mechanical ventilation; these five patients experienced discomfort whilst receiving mechanical ventilation, although none recorded any pain.

Promotion of safety and security

The majority of patients were pleased to leave the ICU, although it was frequently commented that this was because it signified progress in their recovery. The remainder expressed concerns about leaving the perceived security of the high patient:nurse ratio in the ICU environment to return to the general wards.

Discomforts and anxieties

Noise and difficulty in sleeping were the principal concerns in the propofol group. Discomfort on the ventilator was a major concern in those receiving dexmedetomidine, although it only occurred in three patients.

Discussion

This study and previous work[6] have shown dexmedetomidine to be an effective and safe agent for use as postoperative sedation in the ICU. Unlike previous studies, this one sought to compare the new agent dexmedetomidine with propofol, one of the established i.v. sedative agents regularly used in the ICU. An equivalent depth of sedation between dexmedetomidine and propofol in the ICU was achieved, with the advantage that the opioid requirement was reduced by over 50% in patients who received dexmedetomidine.

It is difficult to quantify the cooperation and ease of management seen with patients sedated with dexmedetomidine in the ICU, which presumably reflects only mild cognitive impairment. This may explain the ease and speed of extubation after dexmedetomidine infusions. Although extubation times were similar in the groups, a longer extubation time would have been predicted with dexmedetomidine from volunteer pharmacokinetic data,[14–16] as the elimination half-life of propofol[17] is approximately three times shorter (30–60 min for propofol *vs* 100–150 min for dexmedetomidine). In fact, dexmedetomidine can be continued safely over the extubation period.[7] According to our results, the sample size in this study had an 80% power of detecting a 40% difference in extubation times between the two groups (α-value 0.05). It is also important to note that species-specific hypoxia,[7] seen particularly in sheep given dexmedetomidine, does not occur in humans (Table 2).

The haemodynamics of dexmedetomidine is predictable from the pharmacology of α_2 adrenoceptor agonists, and has been confirmed from previous studies in volunteers,[18 19]

Table 2 Mean (SD) mechanical ventilation variables and arterial blood gases for the first 8 h period of intubation and mechanical ventilation in patients sedated with dexmedetomidine (D) and propofol (P). n=10 in both groups except at 8 h, when n=8 and n=7 in the dexmedetomidine and propofol groups respectively. RR = respiratory rate, TV = tidal volume; $P_{\max}$ = maximum airway pressure; PEEP = positive end-expiratory pressure; Pa_{CO_2} arterial P_{CO_2}; Pa_{O_2}/FI_{O_2} = arterial/inspired oxygen ratio, BE = base excess *P=0.003. propofol *vs* dexamedetomidine group at that time point

	Baseline		2 h		4 h		6 h		8 h	
	D	P	D	P	D	P	D	P	D	P
RR (min^{-1})	13 (1)	14 (2)	14 (1)	14 (1)	14 (2)	14 (2)	13 (3)	14 (2)	14 (3)	14 (3)
TV (ml)	579 (122)	624 (102)	596 (91)	619 (111)	606 (95)	640 (152)	622 (111)	585 (89)	599 (154)	635 (111)
Pmax (cm H_2O)	24 (3)	25 (3)	25 (3)	25 (3)	25 (3)	25 (3)	24 (3)	24 (2)	24 (3)	25 (2)
PEEP (cm H_2O)	5 (1)	7 (3)	5 (1)	7 (3)	5 (1)	6 (2)	5 (1)	6 (1)	5 (1)	6 (1)
pH	7.32 (0.10)	7.36 (0.07)	7.35 (0.06)	7.33 (0.11)	7.37 (0.08)	7.33 (0.08)	7.38 (0.08)	7.33 (0.10)	7.39 (0.08)	7.34 (0.04)
Pa_{CO_2} (kPa)	4.9 (0.9)	5.2* (0.3)	4.6 (0.4)	5.8* (1.0)	4.7 (0.6)	5.6* (1.2)	4.5 (0.4)	5.8* (1.5)	4.6 (0.8)	5.6* (0.3)
Pa_{O_2}/FI_{O_2}	43 (13)	29 (14)	45 (12)	38 (14)	50 (14)	33 (11)	45 (8)	32 (8)	42 (12)	37 (10)
BE	−6 (4)	−3 (4)	−5 (4)	−4 (3)	−4 (3)	−3 (3)	−4 (4)	−3 (3)	−4 (3)	−3 (3)

Table 3 Mean (SD) biochemical and haematological variables at baseline and 24 and 48 h after commencement of the study in the dexmedetomidine and propofol groups. There were significant within-group differences in sodium, urea and creatinine concentrations for the dexmedetomidine group and in the leucocyte count for the propofol group over the 48 h study period Significant within-group differences were also present in the platelet counts for both groups (P<0.01) PTT = prothrombin ratio; KCCT = kaolin cephalin clotting time. *P<0.05; **P<0.01 compared with baseline

	Dexmedetomidine			Propofol			*P* value
	Baseline	24 h	48 h	Baseline	24 h	48 h	(between groups)
Biochemical variables							
Na (mmol litre^{-1})	138 (4)	142 (4)*	143 (3)**	140 (3)	142 (3)	142 (5)	0.84
K (mmol litre^{-1})	4.7 (0.9)	4.2 (0.4)	4.0 (0.5)	4.2 (0.4)	4.4 (0.5)	4.4 (0.5)	0.85
Urea (mmol litre^{-1})	5.0 (2.6)	6.3 (2.5)	8.0 (4.1)*	5.2 (2.7)	5.9 (4.8)	6.7 (5.3)	0.78
Creatinine (μmol litre^{-1})	86 (20)	99 (38)	113 (48)*	83 (22)	97 (35)	101 (40)	0.68
Bilirubin (μmol litre^{-1})	27 (36)	28 (41)	21 (28)	12 (5)f	16 (12)	16 (11)	0.37
Alanine aminotransferase (IU litre^{-1})	23 (17)	26 (25)	26 (30)	38 (48)	46 (71)	47 (71)	0.93
Alkaline phosphatase (IU litre^{-1})	87 (113)	38 (19)	46 (28)	55 (31)	39 (22)	53 (18)	0.64
Albumin (g litre^{-1})	24 (14)	18 (7)	18 (6)	24 (11)	17 (7)	21 (6)	0.67
Calcium (mmol litre^{-1})	2.10 (0.20)	2.09 (0.19)	2.08 (0.19)	2.08 (0.20)	1.97 (0.19)	1.98 (0.19)	0.27
Phosphate (mmol litre^{-1})	1.25 (0.18)	1.22 (0.32)	1.07 (0.36)	1.12 (0.49)	1.27 (0.48)	1.17 (0.43)	0.95
Haematological variables							
Haemoglobin (g dl^{-1})	11.3 (1.4)	10.8 (0.9)	10.5 (0.6)	11.9 (2.2)	10.9 (0.8)	11.3 (0.9)	0.21
Leucocytes (× 10^9 litre^{-1})	8.1 (1.9)	13.0 (10.0)	12.7 (5.4)	8.9 (2.9)	9.3 (2.9)	11.3 (2.4)*	0.44
Platelets (× 10^9 litre^{-1})	239 (88)	160 (59)**	160 (84)**	208 (64)	151 (77)**	155 (68)**	0.63
PTT	1.0 (0.2)	1.2 (0.2)	1.2 (0.2)	1.0 (0.2)	1.1 (0.2)	1.1 (0.2)	0.13
KCCT (s)	47 (7)	48 (3)	51 (7)	48 (9)	55 (9)	47 (5)	0.67
Thrombin time (s)	13 (2)	12 (2)	12 (2)	13 (3)	16 (6)	13 (1)	0.34

patients under anaesthesia[20 21] and, more recently, ICU patients.[6] Great interest exists in the comparative difference in cardiovascular responses between dexmedetomidine and other sedative agents. Vasodilatation, which manifests itself as a reduction in arterial pressure, is a feature of sedation with both propofol[11 22 23] and dexmedetomidine.[6] In this study, equipotent sedative doses of these agents, infused in patients with similar central venous filling pressures, resulted in equivalent mild reductions in arterial pressures. The numerous adverse cardiovascular events seen previously with the loading infusion of dexmedetomidine[6] were not seen in this study. This was achieved by reducing the dexmedetomidine dose during the loading infusion. However, the significantly lower heart rates seen with dexmedetomidine in comparison with patients receiving propofol may lower the risk of ischaemic events during the stressful ICU episode, in particular over the extubation period. Previous studies have shown sustained higher heart rates (mean 90 beats min^{-1}) similar to those in this study for patients receiving propofol in the ICU.[11 22 23]

No differences in measured biochemical and haematological variables were seen between the groups. A few within-group differences were seen (and would be expected) after extensive surgery. The median urine output was greater for patients receiving dexmedetomidine, although this was not statistically significant. Previous experimental data have shown that α_2 adrenoceptor agonists promote diuresis and natriuresis. The mechanisms proposed include inhibition of antidiuretic hormone[24] and/or atrial natriuretic peptide release.[25] However, the small increase in urea and creatinine seen in this study do not support any renal protective effects of dexmedetomidine.

The median BIS values of patients receiving either dexmedetomidine or propofol infusions in this study suggest

Table 4 Patient experiences in the ICU. Numbers of patients are shown. *$P=0.023$ compared with dexmedetomidine group

	Dexmedetomidine (n=10)	**Propofol** (n=10)
Memory of ICU experiences		
Accurate recording of length of ICU stay	8	2*
Accurate recording of duration of mechanical ventilation	3	2
Promotion of safety and security		
Efficient and sympathetic nursing and medical staff	10	10
Pleased to leave ICU	6	7
ICU stay described as pleasant overall	10	6
Discomforts and anxieties		
Tracheal suctioning	2	1
Handling and movement of various lines and tubes	2	0
Noise	1	4
Conversations in the ICU	0	1
Difficulty in sleeping	3	7
Discomfort from ventilator	3	2
Pain	0	0
Being on a ventilator	4	2
Fear of procedures	1	0
Being washed	1	1

a low incidence of recall.[10] Although many patients who received dexmedetomidine were able to record their total length of ICU stay accurately, far fewer could recall the duration of mechanical ventilation, presumably because of the use of sedative agents. It may be that any amnesic actions of dexmedetomidine disappear rapidly after discontinuation of the infusion. However, in both groups a few patients were able to remember the period during which they were mechanically ventilated and sedated, and it would therefore be prudent not to use dexmedetomidine alone in patients who are also receiving neuromuscular block agents.

A modified Hewitt questionnaire was used in this study as it has been used by several researchers[3 26 27] to determine patients' recollections, anxieties and discomforts within a few days of their ICU stay. Although patients appeared calm and cooperative to the clinician whilst sedated with dexmedetomidine, this may not reflect their perception of this time in the ICU. Reassuringly, all patients who received dexmedetomidine described their ICU stay as pleasant and were not resentful of any awareness. Sleep, anxiety concerning the ventilator, pain and noise featured prominently in both groups as the major discomforts and anxieties whilst in the ICU, and this again parallels previous studies.[3–5] Interestingly, lack of sleep appeared to be less of a problem in patients receiving dexmedetomidine, and it may be that 'pharmacological' sleep with dexmedetomidine resembles normal physiological sleep. This is relevant because deprivation may correlate with the development of ICU psychosis.[28]

In conclusion, dexmedetomidine appears to be a safe and acceptable ICU sedative agent when both the clinician's and patient's perspectives are considered. Depth of sedation is similar to that given by propofol and the extubation time is equally rapid, despite the longer elimination half-life of dexmedetomidine. The cardiovascular response of patients sedated with dexmedetomidine is similar to that of patients sedated with equipotent doses of propofol, except that those receiving dexmedetomidine do not increase their heart rate. These properties, combined with the analgesic qualities and lack of respiratory depression seen with dexmedetomidine, have advantages for patients at risk from myocardial ischaemia.

Appendix

Questionnaire based on that of Hewitt[3]

We would be grateful if you could answer the following questions detailing your recent experiences in the Intensive Care Unit. Please insert a number in the relevant box or circle the most appropriate phrase.

1 How long do you think you were in intensive care?
Hours
Days
No idea

2 How long do you think you were on the breathing machine in intensive care?
Hours
Days
No idea
Never

3 When on the breathing machine did you feel
Pain
Discomfort

4 Which of the following descriptions best describes the nursing staff?
Efficient and sympathetic
Efficient but not always thoughtful enough
Too attentive
Too distant
Unable to remember

5 Which of the following descriptions best describes the doctors?
Efficient and considerate
Efficient but did not explain things enough
Too disturbing and discussed too many worrying medical details in front of you
Not around enough when you felt you needed treatment or explanations
Unable to remember

6 Do you think your relatives or friends were allowed to see you enough?
Yes
No

received adequate explanation about your progress?
    Yes
    No

7 Did any/some/all of the following aspects of intensive care upset you a lot?
  Physiotherapy
  Suction down breathing tubes
  Handling and movement of various tubes
  Amount of noise
  Alarms
  Conversations in the ITU (medical or non-medical)
  Amount of machinery
  Difficulty in resting or sleeping
  If you circled this aspect of care, was the difficulty due to any or all of the following?
  Pain, discomfort, noise, light, anxiety
  Pain
  Being on the breathing machine
  Fear of insertion of lines and tubes
  Fear of machine failure
  Being washed
  Any other worries—please state

8 Were you pleased to leave intensive care and return to your ward?
    Yes
    No

9 What are your overall feelings about intensive care?
  Pleasant
  Unpleasant

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Influence of equianaesthetic concentrations of nitrous oxide and isoflurane on regional cerebral blood flow, regional cerebral blood volume, and regional mean transit time in human volunteers

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Nitrous oxide and isoflurane have cerebral vasodilatory effects. The use of isoflurane in neuroanaesthesia is widely accepted, whereas the use of nitrous oxide in neuroanaesthesia is still the subject of debate. In the present study, contrast-enhanced magnetic resonance (MR) perfusion measurement was used to compare the effects of 0.4 MAC nitrous oxide (n=9) and 0.4 MAC isoflurane (n=9) on regional cerebral blood flow (rCBF), regional cerebral blood volume (rCBV) and regional mean transit time (rMTT) in spontaneously breathing human volunteers. Nitrous oxide increased rCBF and rCBV in supratentorial regions more than did isoflurane. Isoflurane, by contrast, increased rCBF and rCBV in basal ganglia more than did nitrous oxide. An increased rMTT was caused by a relatively greater increase in rCBV than in rCBF supratentorially by isoflurane and infratentorially by nitrous oxide. In conclusion, nitrous oxide increases rCBF and rCBV predominantly in supratentorial grey matter, whereas isoflurane increases rCBF and rCBV predominantly in infratentorial grey matter.

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Keywords: anaesthetics volatile, isoflurane; anaesthetics gases, nitrous oxide; brain, blood volume; brain, blood flow, regional mean transit time; humans

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Nitrous oxide has been used in anaesthesia for more than a century[1] because of its dose-dependent analgesic and anaesthetic properties.[2] The use of nitrous oxide in certain situations (e.g. intracranial surgery), however, is still the subject of debate as the drug is a potent cerebral vasodilator.[3] In combination with potent inhalational anaesthetics, e.g. isoflurane, nitrous oxide is known to increase mean cerebral blood flow (CBF).[4] By contrast, isoflurane, which has become the anaesthetic of choice for neuroanaesthesia,[5] was shown to decrease global CBF in a dose-dependent manner in animals.[6] A systematic study comparing nitrous oxide with isoflurane for their regional effects on CBF and simultaneously on regional cerebral blood volume (rCBV) in humans has not yet been conducted.

The present study used contrast-enhanced magnetic resonance imaging (MRI) perfusion measurements to investigate the influence of nitrous oxide and isoflurane on regional cerebral blood flow (rCBF), rCBV and regional mean transit time (rMTT). rMTT was used to analyse changes in rCBV in relation to changes in rCBF.

Methods

After approval by the local university ethics committee and written informed consent, 20 right-handed, non-smoking male volunteers (ASA physical status I) with no history of drug or alcohol abuse underwent MRI measurement of contrast-enhanced cerebral perfusion on two consecutive days. For each volunteer, the order of measurements (e.g. control and test-drug measurement), which were separated by 24 h, was allocated randomly. The volunteers were then allocated randomly to receive either isoflurane or nitrous oxide as the test drug.

Wearing a closely fitting face-mask, the volunteers breathed to achieve normocarbia [end-tidal carbon dioxide concentration (E'_{CO_2}) 40 mm Hg, F_{IO_2} 0.5] during the control measurement and administration of isoflurane [fraction of

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expired isoflurane 0.45 (SD 0.02)%; 0.4 MAC][7] (n=10) or nitrous oxide [fraction of expired nitrous oxide 45 (2)%; 0.4 MAC][8] (n=10). A minimum of 10–15 min was allowed for stabilization of the end-tidal concentration of either anaesthetic before contrast-enhanced MRI perfusion measurement.The volunteers had been trained both by verbal instruction and by watching the capnographic trace of the monitor on the day before the MRI session. During the experiment, breathing at a constant E'_{CO_2} (e.g. 40 mm Hg) was supported by voice command when necessary. The fraction of inspired and expired isoflurane, nitrous oxide, oxygen (FI_{O_2}, FE'_{CO_2}, E'_{CO_2}, respiration rate, non-invasive mean arterial blood pressure (MAP) and pulse oximetry haemoglobin saturation (Sp_{O_2}) were monitored (S/5 MRI-Monitor™, Datex-Ohmeda, Helsinki, Finland). Quick Cal calibration gas (Ref. 755582; Datex) was used to calibrate the monitor.

MRI measurements were performed with a 1.5-tesla whole-body scanner (Magnetom Vision; Siemens, Erlangen, Germany) using a standard circular polarized head-coil. Single-shot echoplanar imaging (EPI) was performed with a repetition time of 2 s and an echo time of 64 ms. An acquisition matrix of 64×128 (field of view 22×22 cm, in-plane resolution 1.7×3.4 mm) was used. The slice thickness was set to 5 mm (slice gap 1.25 mm) and 15 slices were measured simultaneously. A paramagnetic contrast agent gadolinium-diethylene triamine pentaacetic acid (Gd-DTPA, 0.1 mmol kg^{-1}) was injected into an antecubital vein at the rate of 9 ml s^{-1} using an MR-compatible power injector (Spectris; Medrad, Pittsburgh, PA, USA). EPI scans (n=60) were performed at 2-s intervals to cover the entire passage of the contrast agent through the brain. Six scans (6/60 scans) taken before injection were used as the baseline.

rCBV and rCBF were calculated by a blinded investigator in regions of interest. In each subject, regions of interest were outlined freehand bilaterally in white and in grey matter (frontal, parietal, occipital, striatal and thalamic) on CBV maps (Fig. 1). Outlining regions of interest on corresponding anatomical T_2-weighted scans is not possible as EPI T_2*-weighted contrast-enhanced perfusion scans have a known geometric distortion. In order to check the regions of interest for correct anatomical position, they were copied into the EPI T_2*-weighted scans acquired before contrast media application. The definition of regions produced in this way is reliable and reproducible and is not biased to high signal areas on the CBV maps. Furthermore, varying partial volume effects as a result of the inclusion of white and grey matter in regions allocated primarily to one category, which could account for some of the differences between the regions, were minimized. Corresponding regions of interest contained similar numbers of pixels.

The basic concept used to determine CBV and CBF was described by Ostergaard *et al.*[9–11] An improved gamma variate fit was used to reduce underestimation of the arterial input function, which otherwise leads to overestimation of CBV and CBF values.[12]

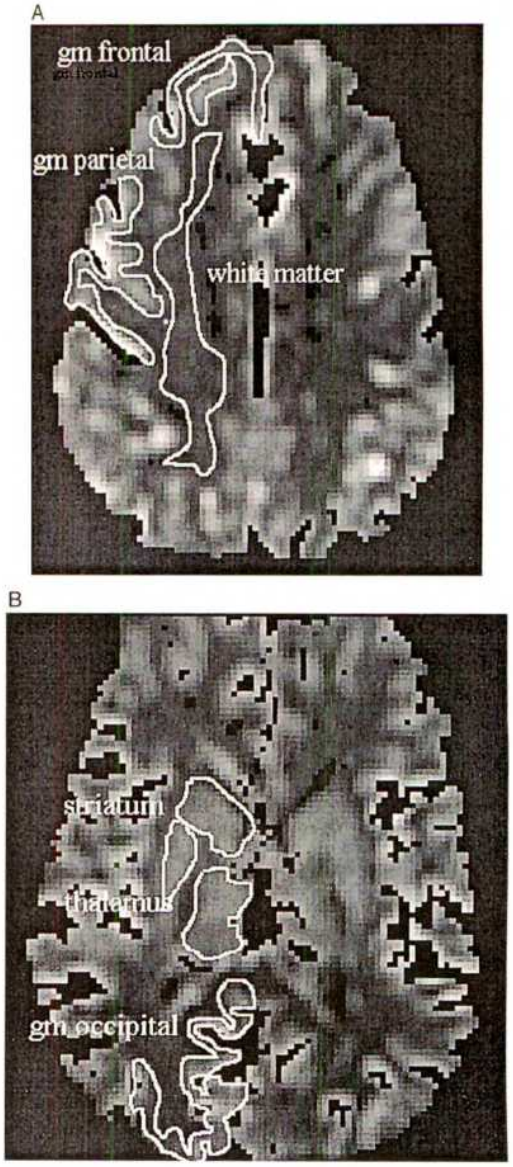

Fig 1 Representative CBV map during administration of isoflurane (0.4 MAC) showing regions of interest for evaluation of right hemisphere white matter and parietal (gm parietal), frontal (gm frontal) (A), thalamic (thalamus), striatal (striatum) and occipital (gm occipital) (B) grey matter rCBV.

After correction for the density of brain tissue,[13] rCBF values are given in ml 100 g^{-1} min^{-1} and rCBV values in ml 100 g^{-1}.

MTT, which defines the average time that any particle of tracer, e.g. contrast medium, remains within the region of interest,[14] was calculated with the equation:

$$\mathrm{rMTT} = \frac{\mathrm{rCBV}}{\mathrm{rCBF}} \times 60$$

Values for rMTT are given in seconds.

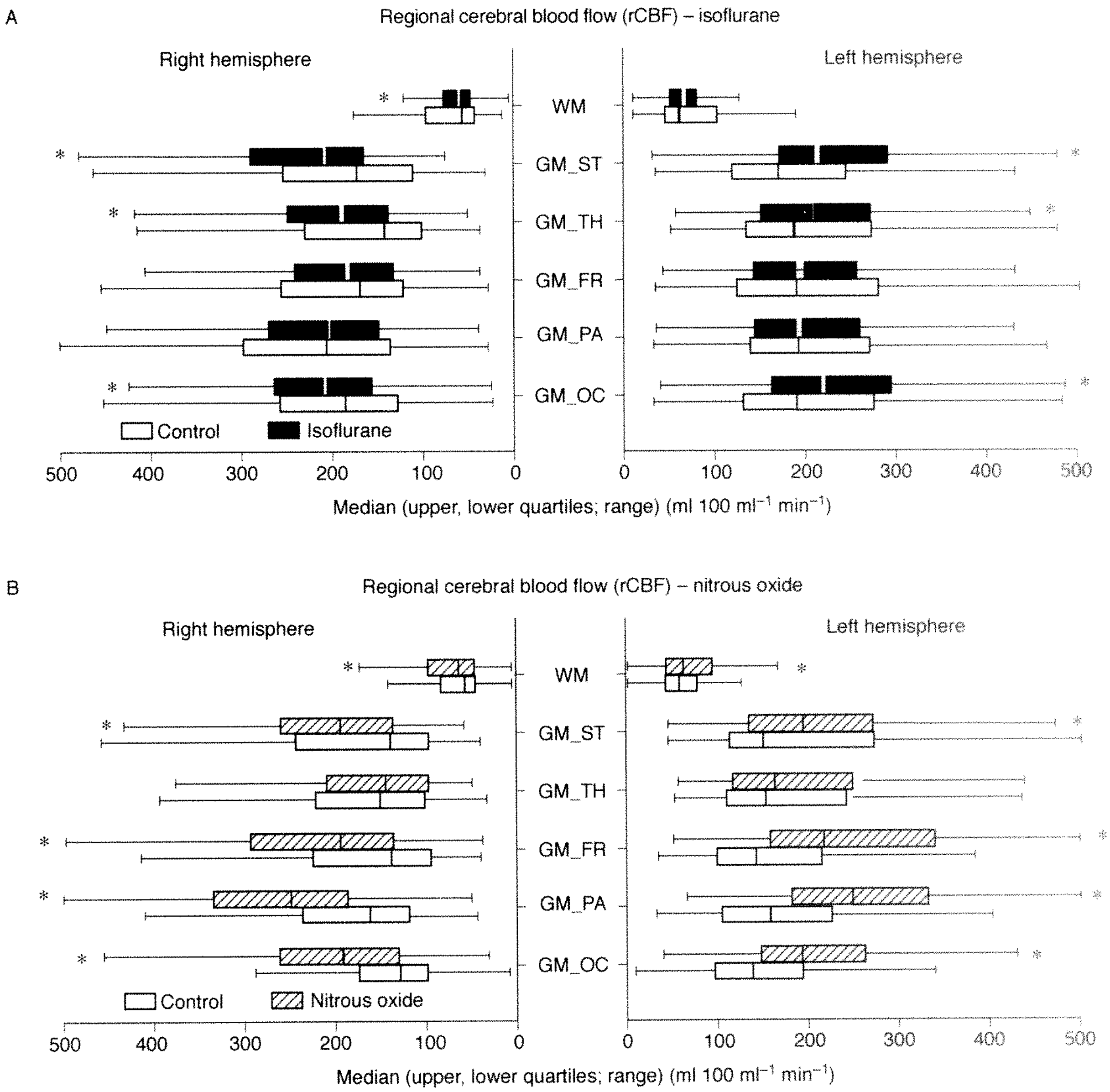

Fig 2 rCBF in white matter (WM) and grey matter [striatal (GM_ST), thalamic (GM_TH), frontal (GM_FR), parietal (GM_PA), occipital (GM_OC)] during control and administration of isoflurane (0.4 MAC) (*n*=9) (A) and during control and administration of nitrous oxide (0.4 MAC) (*n*=9) (B). Data are presented as boxplots [e.g. median (upper, lower quartiles; range]. $*P<0.05$.

Statistical analysis

Data are presented as boxplots [e.g. median (upper, lower quartiles; range)]. Data were tested for normality with the Kolmogorov–Smirnov test. As the data were not normally distributed, within-group comparison was performed with a stable non-parametric test (e.g. the Mann–Whitney *U*-test), which also considered the similar, but not identical, numbers of pixels in comparable regions (e.g. unpaired test). A value of $P<0.05$ was considered statistically significant. Presentation of percentage changes in rCBF (Δ-rCBF), percentage changes in rCBV (Δ-rCBV) and percentage changes in rMTT (Δ-rMTT) are merely descriptive. Differences between the agents in Δ-rCBF, Δ-rCBV and Δ-rMTT were not tested for significance.

Results

All volunteers [*n*=20; age 26 (20–30) yr; weight 77 (SD 3) kg; height 179 (5) cm] completed the study without complication. Because of motion artefacts, measurements were not obtainable in volunteer no. 8 in the nitrous oxide group (1/10) and in volunteer no. 1 in the isoflurane group (1/10).

Responsiveness to verbal command, which was necessary once or twice in each volunteer in order to maintain normocapnia, was sustained during isoflurane (*n*=9) and nitrous oxide (*n*=9) administration. The contrast-enhanced perfusion measurement was commenced only after verbal command had produced stable normocapnia, so that no

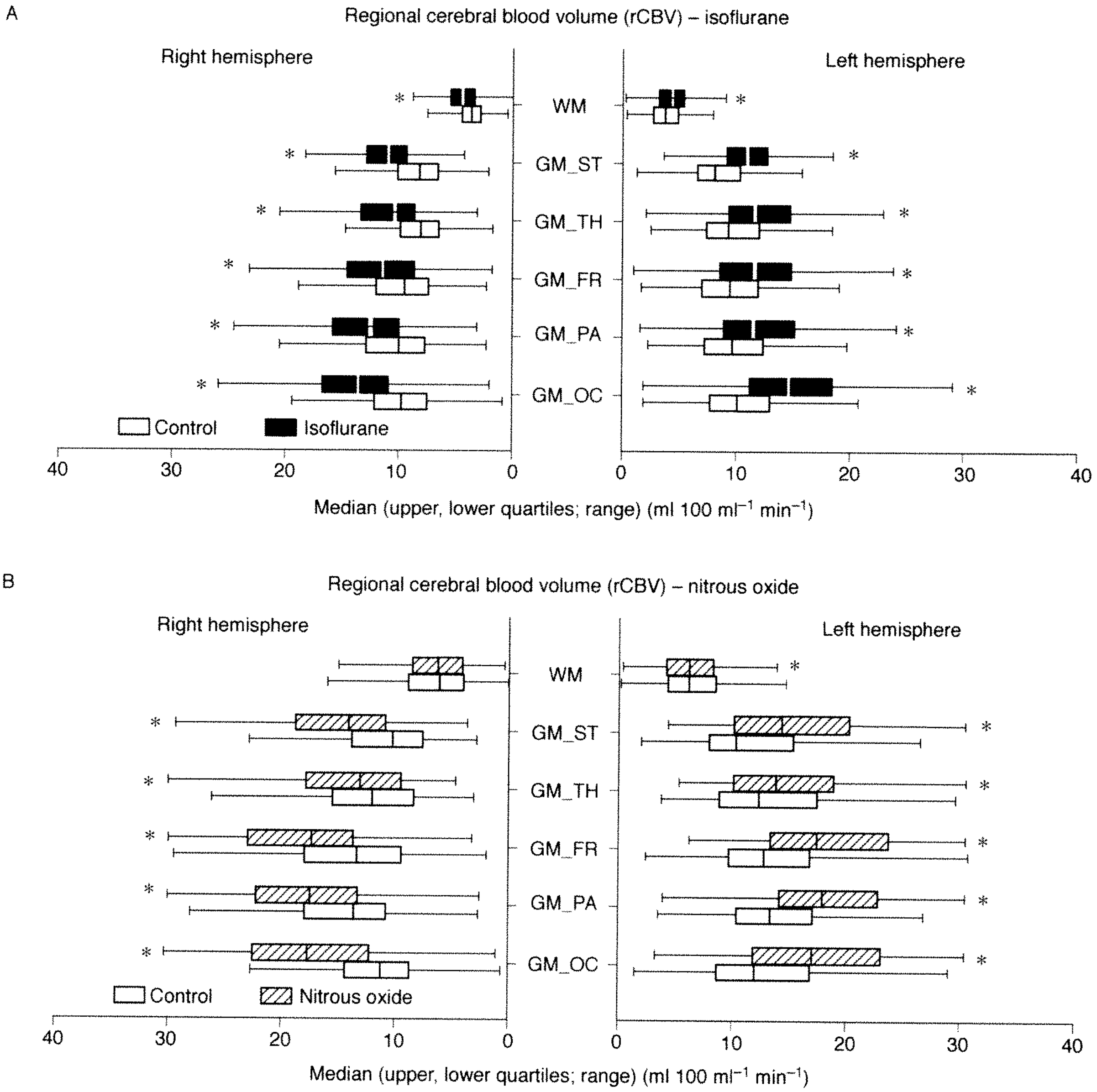

Fig 3 rCBV in white matter (WM) and grey matter [striatal (GM_ST), thalamic (GM_TH), frontal (GM_FR), parietal (GM_PA), occipital (GM_OC)] during control and administration of isoflurane (0.4 MAC) (*n*=9) (A) and during control and administration of nitrous oxide (0.4 MAC) (*n*=9) (B). Data are presented as boxplots [e.g. median (upper, lower quartiles; range)]. *$P<0.05$.

further verbal stimulation was needed during perfusion measurement.

Haemodynamic (heart rate, MAP) and respiratory (Sp_{O_2}, E'_{CO_2}, respiratory rate) variables were influenced neither by isoflurane nor by nitrous oxide.

rCBF

Isoflurane increased occipital but not frontal or parietal grey matter rCBF (Fig. 2A), whereas nitrous oxide increased rCBF in all of these regions (Fig. 2B). In the basal ganglia, except for the right hemispheric striatum, however, isoflurane increased rCBF more than did nitrous oxide (Fig. 3A and B).

rCBV

Both isoflurane (Fig. 4A) and nitrous oxide (Fig. 4B) increased grey matter rCBV in practically all of the regions studied. In detail, nitrous oxide increased rCBV in the frontal and parietal grey matter more than did isoflurane. Right hemisphere occipital rCBV, however, was similarly increased by the two drugs. Both drugs increased striatal rCBV, whereas isoflurane increased thalamic rCBV more than did nitrous oxide (Fig. 5A and B).

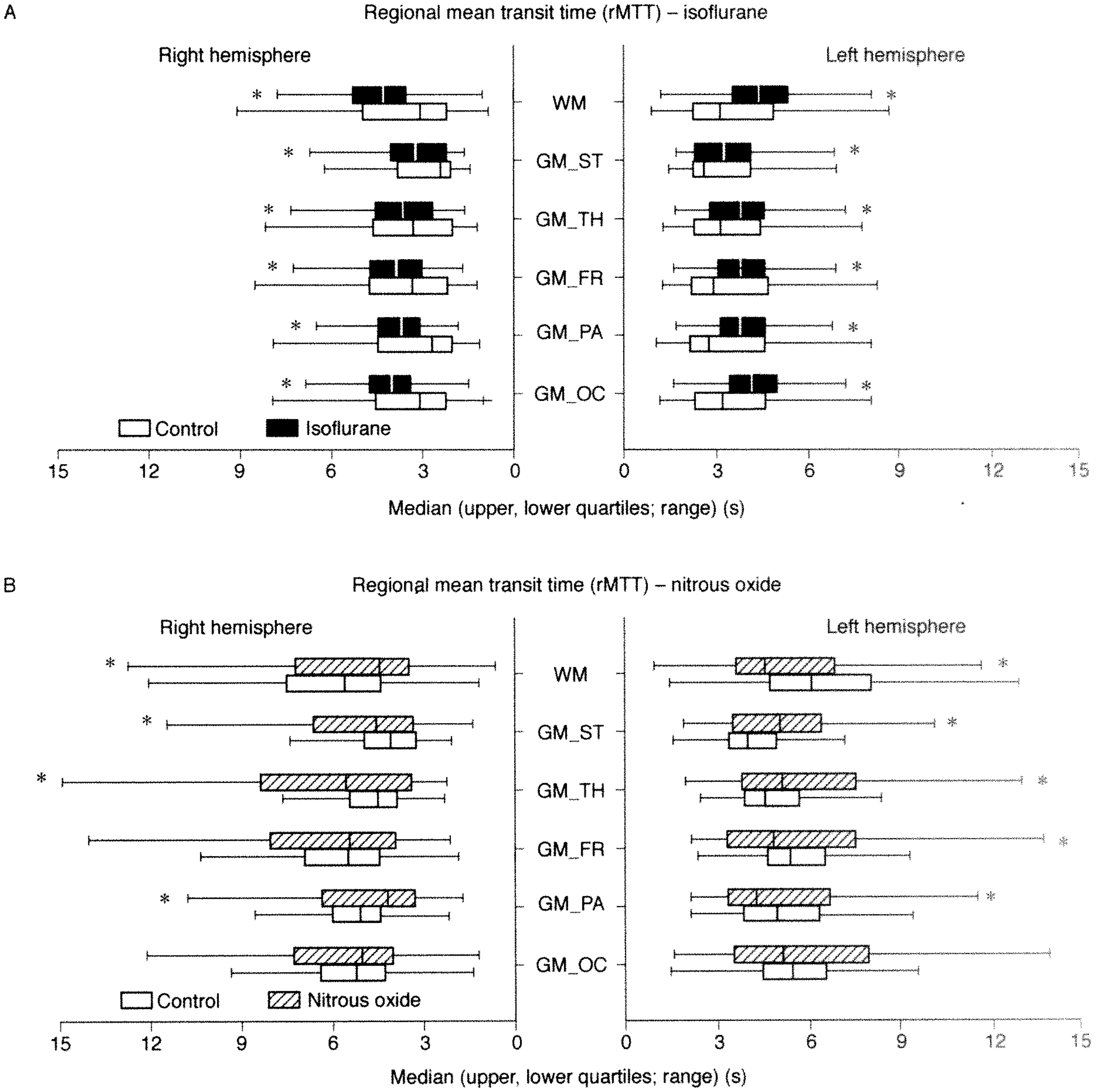

Fig 4 rMTT in white matter (WM) and grey matter [striatal (GM_ST), thalamic (GM_TH), frontal (GM_FR), parietal (GM_PA), occipital (GM_OC)] during control and administration of isoflurane (0.4 MAC) (n=9) (A) and during control and administration of nitrous oxide (0.4 MAC) (n=9) (B). Data are presented as boxplots [e.g. median (upper, lower quartiles; range)]. *P<0.05.

rMTT

Isoflurane (Fig. 6A) and nitrous oxide (Fig. 6B) increased grey matter rMTT in most regions. Isoflurane increased rMTT in the frontal, parietal and occipital grey matter more than did nitrous oxide, which decreased parietal rMTT. In contrast, in the basal ganglia nitrous oxide increased rMTT bilaterally more than did isoflurane (Fig. 7A and B).

Discussion

Nitrous oxide increased rCBF, rCBV and rMTT predominantly in supratentorial regions, whereas isoflurane produced predominantly infratentorial increases. In detail, isoflurane increased occipital grey matter rCBF, which has also been reported by Reinstrup *et al.*[15] The concomitant unchanged frontal/parietal grey matter rCBF indicates a reversal of the anterior–posterior gradient in rCBF observed in normal resting-state studies.[16] A similar reversal of the anterior–posterior gradient in rCBF was reported during coma[17] and sleep.[18] Therefore, the isoflurane-induced reversal of the anterior–posterior gradient in rCBF seen in the present study might well reflect an altered level of consciousness.

Like isoflurane, nitrous oxide increased occipital grey matter rCBF in our volunteers, but no reversal of the anterior–posterior gradient in rCBF was found, as the greatest effect of nitrous oxide on rCBF was found in the

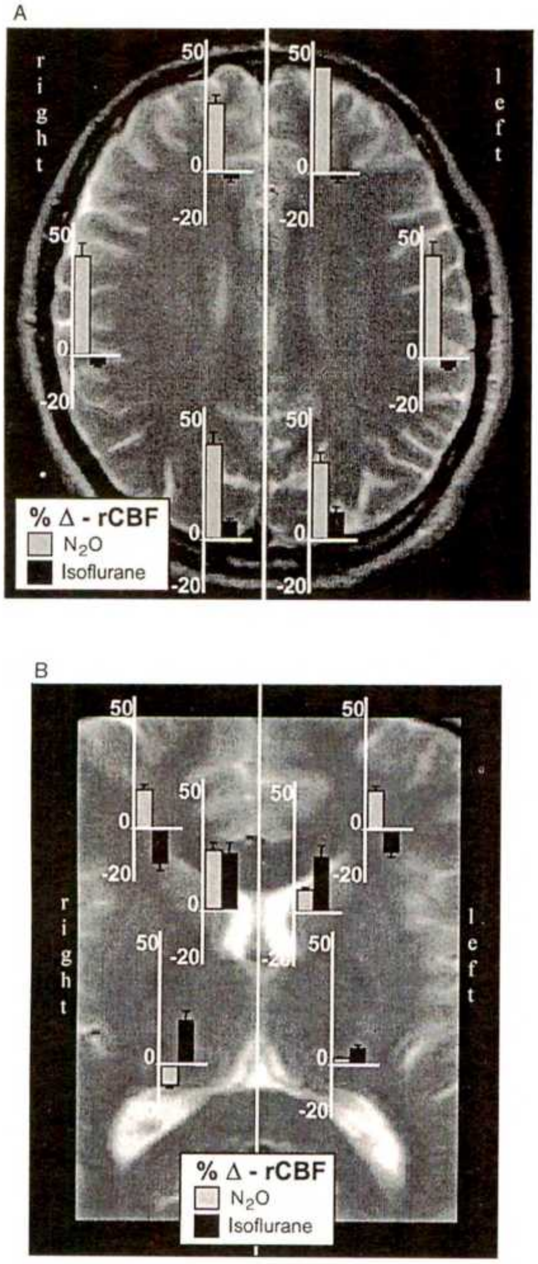

Fig 5 Percentage changes in rCBF in frontal, parietal, occipital grey matter (A) and in striatal and thalamic grey matter and in white matter (B) during administration of isoflurane (0.4 MAC) (*n*=9) or nitrous oxide (0.4 MAC) (*n*=9). Data are mean ± SEM.

frontal and parietal grey matter regions. A similar increase in frontal rCBF has also been reported for nitrous oxide.[19]

It has been proposed that nitrous oxide causes disinhibition of frontal cortical activity,[19] and this may prompt an exaggerated frontal distribution of rCBF, whereas isoflurane typically causes reversal of the anterior–posterior gradient in rCBF. Without psychological tests, however, it is not possible to establish a relationship between a drug-specific pattern of rCBF changes and a drug-specific altered level of consciousness in humans.

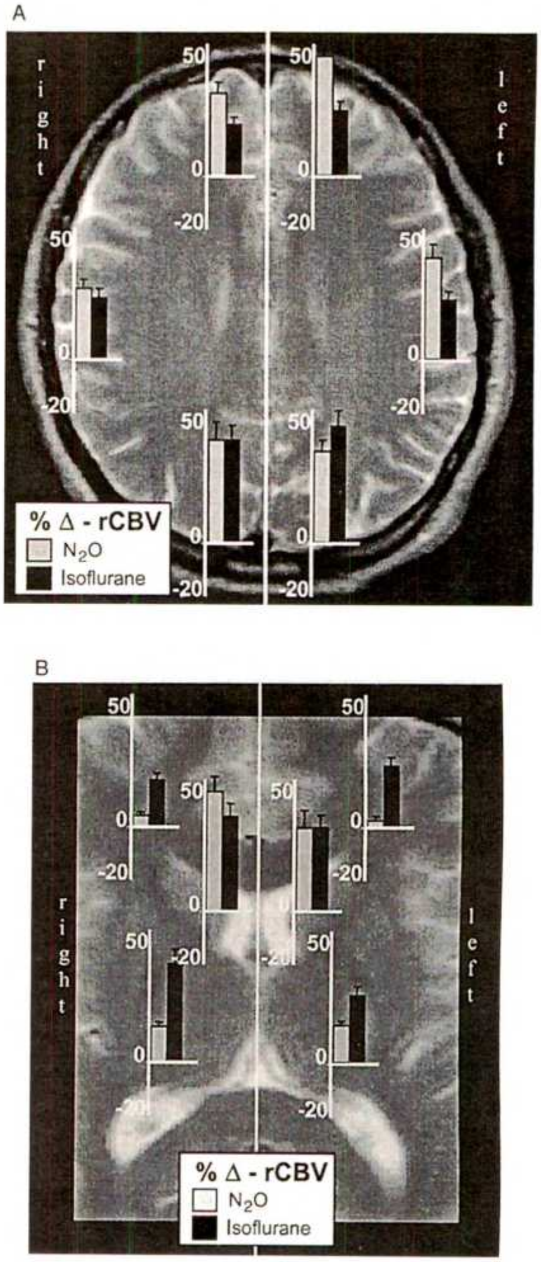

Fig 6 Percentage changes in rCBFV in frontal, parietal, occipital grey matter (A) and in striatal and thalamic grey matter and in white matter (B) during administration of isoflurane (0.4 MAC) (*n*=9) or nitrous oxide (0.4 MAC) (*n*=9). Data are mean ± SEM.

In the infratentorial regions, isoflurane increased thalamic and striatal grey matter rCBF more than did nitrous oxide. A similar redistribution of rCBF to subcortical regions during isoflurane administration was reported in humans[4 15] and animals.[20] Although observed, the increase in rCBF in these regions was clearly less pronounced after nitrous oxide.

Nitrous oxide increased rCBV in frontal and parietal grey matter more but in infratentorial grey matter less than did isoflurane. These heterogeneous increases in rCBV during

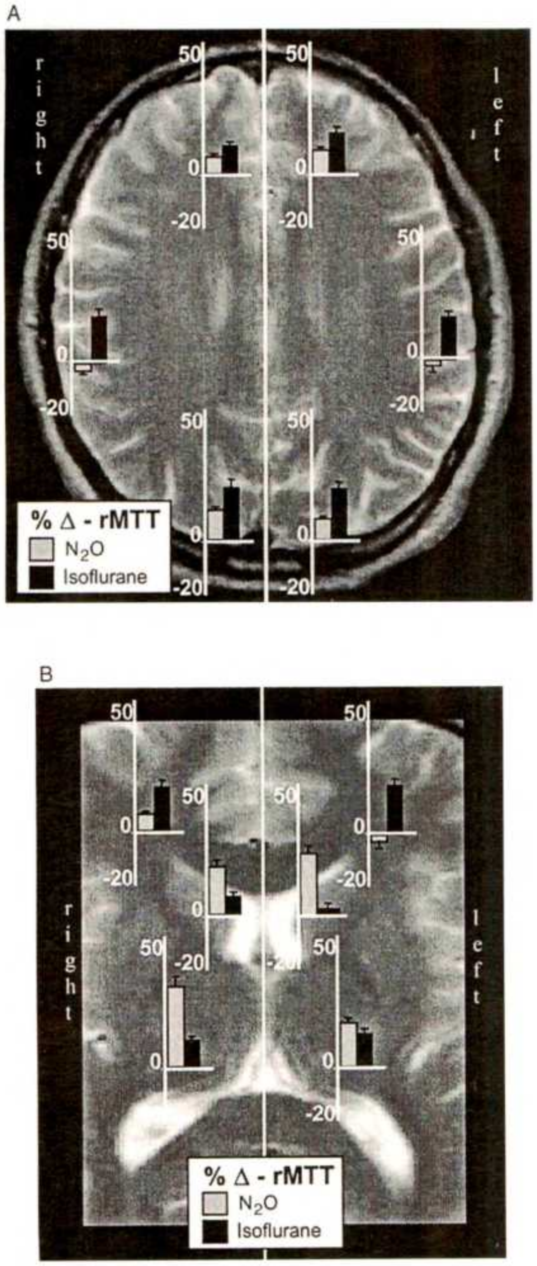

Fig 7 Percentage changes in rMTT in frontal, parietal, occipital grey matter (A) and in striatal and thalamic grey matter and in white matter (B) during administration of isoflurane (0.4 MAC) (n=9) or nitrous oxide (0.4 MAC) (n=9). Data are mean and SEM.

administration of nitrous oxide and isoflurane demonstrate that these drugs are not simple vasodilators like hypercapnia, which causes a more uniform increase in rCBV.[21]

To further analyse changes in rCBV and rCBF, we used rMTT. rMTT defines the average time needed by a tracer to transit the region of interest.[14] Because rMTT equals the ratio of rCBV to rCBF, any increase in rMTT (e.g. in the present study during nitrous oxide and isoflurane administration) reflects a relatively greater increase in rCBV than in rCBF. Isoflurane increased supratentorial rMTT more than did nitrous oxide, thereby indicating a greater increase in rCBV than in rCBF. In contrast, the infratentorial increase in rMTT was more pronounced under nitrous oxide. The extent to which drug-specific changes in rCBF and rCBV, as seen in the present study, are caused by direct vasodilatation and/or metabolically mediated effects on cerebral haemodynamics awaits further investigation. In this regard, it is a limitation of the present study that, during administration of nitrous oxide and isoflurane, metabolic data (obtained, for example, by means of phosphate spectroscopy), were not obtainable with the whole-body MR scanner we used (Magnetom Vision).

In conclusion, we have shown that nitrous oxide specifically increases rCBF and rCBV in supratentorial grey matter, whereas isoflurane specifically increases rCBF and rCBV in infratentorial grey matter.

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Cerebral effects and blood sparing efficiency of sodium nitroprusside-induced hypotension alone and in combination with acute normovolaemic haemodilution

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The combined reduction of oxygen-carrying capacity and perfusion pressure during the combination of acute normovolaemic haemodilution (ANH) and controlled hypotension (CH) raises concerns of hypoperfusion and ischaemic injury to the brain. Forty-two patients undergoing radical prostatectomy were prospectively allocated to receive CH induced by sodium nitroprusside (mean arterial pressure (MAP) 50 mm Hg), a combination of CH+ANH (post-ANH haematocrit 29%; intraoperative MAP 50 mm Hg), or standard anaesthesia (control). Serum levels of the brain-originated proteins neuron-specific enolase (NSE) and protein S-100, blood loss, transfusion requirements, adverse effects, and postoperative recovery profile were compared among the three groups. Intraoperative blood loss in the CH group (mean (SD)) (788 (193) ml) and CH+ANH group (861 (184) ml) was significantly less than in the control group (1335 (460) ml). Significantly fewer total units of allogeneic packed red blood cells (PRBC) were transfused in the patients receiving hypotensive anaesthesia (CH, 3 units; CH+ANH, 2 units; control, 17 units). There was no difference in immediate postoperative recovery profile among the three groups as determined by the emergence from anaesthesia and time to discharge from the postanaesthesia care unit. Serum S-100 protein concentrations increased significantly in all groups from baseline to peak concentrations 2 h postoperatively (CH 0.25 (0.11) µg litre^{-1}; CH+ANH 0.31 (0.12) µg litre^{-1}; control 0.31 (0.10) µg litre^{-1}). A return to baseline values was seen within 24 h postoperatively in all patients. No changes in NSE concentrations were seen. Our observations suggest that CH and CH+ANH were effective in reducing blood loss and transfusion requirements in patients undergoing radical prostatectomy. Increased serum S-100 protein concentrations imply a disturbance in astroglial cell membrane integrity and an increased endothelial permeability of the blood–brain barrier. There were no associations between serum S-100 protein or NSE and adverse cognitive effects. Further work needs to be done to determine the prognostic importance of S-100 protein and NSE as surrogate variables of postoperative cerebral complications.

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Alternatives to the use of allogeneic blood products are increasingly being sought. Controlled hypotension (CH), using continuous infusion of sodium nitroprusside (SNP) and acute normovolaemic haemodilution (ANH) have been proven effective in decreasing operative blood loss and the need for transfusion of allogeneic blood.[1–3] Combining CH with ANH may further reduce the requirements for allogeneic blood.[4] However, the combined use of CH and ANH remains under-utilized, because of the fear that a coexistence of reduced oxygen content and perfusion pressure might lead to hypoperfusion and ischaemic injury to vital organs. The organ most susceptible to hypoxia is the brain. The physiology and limits of cerebral perfusion have been investigated in a variety of clinical and experimental studies.[5–9] Both blood-saving strategies were well tolerated without apparent organ damage, provided that an adequate

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circulatory volume was maintained. Compensatory mechanisms during normovolaemic anaemia, such as increased cardiac output and the redistribution of blood flow to areas of high metabolic demand, provide sufficient blood flow to other organs and preserve tissue normoxia over a wide range of haematocrit.[10] Vital organs such as the brain are characterized by a well functioning pressure-flow autoregulation. It is generally accepted that cerebral blood flow (CBF) remains constant at a mean arterial pressure (MAP) ranging from 50 to 150 mm Hg in normotensive patients. Studies in animals, however, provided some evidence that the superimposition of drug-induced hypotension to severe haemodilution might decrease cardiac output and organ blood flow.[11] Therefore, the adequacy of cerebral perfusion might be affected and ischaemic damage to the brain might occur.

In recent years, specific brain-originated proteins have gained particular attention in the identification of central nervous system (CNS) dysfunction.[12] Protein S-100 serum levels and neuron-specific enolase (NSE) have been studied in various clinical settings as specific biochemical markers for the evaluation of cerebral damage.[13–15] The S-100 protein is a small (molecular weight 21 000 Da) acidic calcium-binding protein and is predominantly found in astrocytes and Schwann cells. It exits in various isoforms, depending on alpha or beta subunit configuration. The beta subunit is highly specific to the brain. Its appearance in the blood indicates brain cell damage and an increased permeability of the blood–brain barrier.[12] NSE is an isoenzyme of the glycolytic enzyme enolase, which is present primarily in the cytoplasm of neurones and cells of the amine precursor uptake and decarboxylation system. This protein is a prognostic indicator of hypoxic brain damage after cardiac arrest and resuscitation. Furthermore it may be a useful tool for monitoring brain infarction and intracerebral haemorrhage.[16]

As information is lacking as to how combined CH and ANH modifies serum levels of S-100 protein and neuron-specific enolase, we tested the hypothesis that this hypotensive anaesthetic technique might be associated with a disturbance of neuronal cell integrity and subsequent higher serum concentrations of these brain-originated proteins in comparison with normotensive general anaesthesia. Furthermore, we have investigated whether combining CH with ANH would result in greater blood sparing effects than CH alone.

Methods

The study was approved by the Human Ethics Committee of the hospital and written informed consent was obtained from each patient. We studied prospectively a total of 42 American Society of Anesthesiologists (ASA) class I–III patients undergoing elective radical prostatectomy. Exclusion criteria were ASA class greater than III, liver dysfunction (ALT/AST >40 unit litre^{-1}), renal insufficiency (creatinine >1.5 mg dl^{-1}), haemoglobin concentration less than 12 g dl^{-1}, severe uncontrolled hypertension (systolic pressure >180 mm Hg or diastolic pressure >100 mm Hg receiving medication), a history of myocardial infarction, angina pectoris, and documented coronary artery disease or carotid artery stenosis. All patients were premedicated with midazolam orally 1 h before induction of anaesthesia. Anaesthesia was induced by thiopental, fentanyl and was maintained with fentanyl and desflurane. Rocuronium was used to produce neuromuscular block. The lungs of all patients were ventilated with 50% nitrous oxide in oxygen. Ventilation was adjusted to keep Sa_{O_2} greater than 95% (continuous oximetry) and to maintain PCO$_2$ and pH in the physiological range. Routine intraoperative monitoring included continuous invasive measurement of MAP and central venous pressure (CVP). The patients were allocated randomly to one of three groups. Group 1 (CH, n=14) received CH induced by SNP, group 2 (CH+ANH, n=14) received a combination of ANH and CH. Group 3 (control, n=14), without manipulations, served as control group. ANH in group 2 was carried out after induction of anaesthesia by withdrawing 1000 ml of blood into standard blood collection sets containing citrate–phosphate–glucose with adenine (CPDA-1, Kwasumi, Tokyo, Japan). The identical volume of colloid was given in the form of gelatin (Gelafundin, B. Braun, Melsungen, Germany) to replace withdrawn blood isovolaemically according to the patient's individual CVP before haemodilution. The removed autologous blood was retransfused at the end of the surgical procedure before the patient left the operating room. CH was initiated in groups 1 and 2 at the beginning of bilateral pelvic lymphadenectomy and was completed with wound closure. The SNP doses applied were adjusted to reduce MAP to 50 mm Hg. A threshold of hypotension was defined as a MAP of less than 50 mm Hg in groups 1 and 2, and 70 mm Hg in the control group. Hypotensive episodes were treated by increasing the rate of fluid administration and reducing the concentration of desflurane and/or SNP when necessary. Crystalloids and gelatin were given to maintain CVP at 10–15 mm Hg. A haemoglobin concentration less than 7 g dl^{-1} was defined as the transfusion trigger and mandated the retransfusion of one unit of autologous blood in group 2 or one unit of allogeneic PRBC in groups 1 and 3. Anaesthesia was provided by anaesthetists who were not involved in data analysis.

Times from discontinuation of anaesthetics to eye opening, to trachea extubation, and to orientation (giving one's name and date of birth on request) were recorded. After surgery all patients were observed in the post-anaesthesia care unit (PACU) and the time to eligibility to discharge from the PACU according to Aldrete scoring[17] was also recorded.

Peripheral venous blood samples for S-100 protein and NSE measurements were obtained at induction of anaesthesia (T_0), at the end of surgery (T_1), 2 (T_2), and 24 h (T_3) postoperatively. Serum S-100 protein was analysed with the

Table 1 Patient characteristics and data from the perioperative period Values are expressed as mean (SD), number of patients [range]

	CH+ANH (*n*=14)	**CH (*n*=14)**	**Control (*n*=14)**
Age (yr)	63.3 (6.0) [52–72]	63.2 (5 5) [51–71]	64 5 (7 0) [52–74]
ASA physical status (*n*)			
Class I	4	4	3
Class II	7	8	9
Class III	3	2	2
Height (cm)	171.3 (10.1)	175.6 (8.2)	177 2 (7.2)
Weight (kg)	79.7 (9 0)	78.4 (10 8)	77 0 (6.8)
Duration of surgery (min)	159 (21) [115–185]	147 (23) [112–180]	144 (24) [85–180]
Duration of anaesthesia (min)	210 (18) [180–245]	206 (15) [175–230]	202 (26) [150–250]
Duration of hospitalization (days)	11 (0) [10–14]	11 (1) [10–14]	11 (1) [10–15]

Table 2 Blood loss, use of allogeneic blood, and intraoperative volume replacement Values are expressed as mean (SD), total [range] POD 1, first postoperative day.**P*<0.05 compared with other groups

	CH+ANH (*n*=14)	**CH (*n*=14)**	**Control (*n*=14)**
Intraoperative blood loss (ml)	861 (184) [700–1300]	788 (193) [400–1250]	1335* (460) [500–2200]
Number of patients receiving PRBC	1	1	7*
Cumulative PRBC intraoperative/POD 1 (units)	2	3	17*
Intraoperative volume infusion			
Crystalloids (ml)	3243 (805)	2835 (599)	3014 (1195)
Colloids (ml)	2077* (550)	1056 (379)	1205 (334)

use of a commercially available monoclonal two-site immunoluminometric assay (Lia-mat™ Sangtec™ 100, AB Sangtec Medical, Bromma, Sweden). The Sangtec™ 100 assay uses three monoclonal antibodies to detect the beta subunit of the S-100 protein. The functional detection limit of the assay is 0.02 µg litre^{-1}. Normal values as derived from apparently healthy blood donors were found to be less than 0.12 µg litre^{-1}. The intra-assay coefficient of variation was less than 6%. NSE (normal value <15.2 µg litre^{-1}) was measured with the use of a solid phase enzyme immunoassay (Cobas™ Core NSE EIA II, Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany). The assay uses two highly specific monoclonal antibodies that bind to the γ-subunit of the enzyme. The lower limit of detection of sensitivity of the assay and intra-assay coefficient of variation was 0.1 µg litre^{-1} and less than 4%, respectively. Samples with haemolysis were rejected. Plasma concentrations of cardiac troponin T (TnT; using a commercial monoclonal—monoclonal double antibody and one-step sandwich enzyme immunoassay; Boehringer Mannheim, Germany; normal value <0.1 µg litre^{-1}) were measured as a marker of myocardial ischaemia. During surgery and in the PACU, arterial blood samples were analysed at 30 min intervals for haemoglobin concentration, Pa_{O_2}, Pa_{CO_2}, and pH.

Data are shown as mean (SD). The assumption of normality was checked using the Kolmogorov–Smirnov test. Continuous, normally distributed data were compared using paired and unpaired Student's *t*-test or analysis of variance (ANOVA) for repeated measures. When multiple comparisons were made the Bonferroni correction was applied. Continuous, non-normally distributed data were compared using the Wilcoxon test. Binominal data were compared using chi-squared analysis and Fisher's exact test. Correlations between biochemical marker and variables of postoperative recovery were calculated by using Spearman's rank correlation coefficient. Before the study, the number of patients required in each group was determined after a power calculation according to data obtained from previous studies on the release pattern of protein S-100.[18 19] Although there is no generally accepted normal range for this biochemical marker during CH or combined haemodilution and hypotension, we felt that a 50% increase of protein S-100 concentrations from baseline might be of clinical importance. The approximate SD of protein S-100 values has been found to be 0.13 µg litre^{-1}. The alpha error was set at 0.05 (two-sided) and type II (beta) error was at 0.2. Based on this assumption, 14 patients per group were required.

Results

Of the 48 patients initially screened for the study, six could not be enrolled because they violated one or more of the inclusion and exclusion criteria. Among these were patients with abnormal preoperative laboratory tests (haemoglobin concentration <12 g dl^{-1}) and patients with severe hypertension (diastolic pressure >100 mm Hg). The patients in the three groups were comparable with respect to ASA physical status, biometric data, and to duration of anaesthesia and surgery (Table 1). The duration of hospitalization ranged from 10 to 15 days and was similar among groups (Table 1). Blood loss in the CH group and the CH+ANH group was

Table 3 Haemoglobin (Hgb) concentration, haemodynamic data, and arterial blood gas values HR, heart rate, Pa_{O_2}/Pa_{CO_2}, partial pressure of oxygen/carbon dioxide T_0=baseline, induction of anaesthesia, 90 min=90 min after skin incision; T_1=end of surgery; T_2= 2 h postoperatively, T_3=24 h postoperatively. *$P<0.05$, significantly different from baseline value $^+P<0.05$ compared with other groups

Variable	Group	T_0	90 min	T_1	T_2	T_3
Hgb (g dl^{-1})	CH+ANH	13.7 (1.3)	9.1 (0.9)*+	9.5 (1.0)*	9.7 (0.8)*	9.8 (0.7)
	CH	13.9 (1.0)	11.2 (1.1)*	10.1 (1.3)*	10.3 (0.8)*	10.1 (0.9)
	Control	13.6 (0.9)	10.7 (0.9)*	9.3 (1.3)*	8.7 (0.7)*+	8.9 (1.4) *+
MAP (mm Hg)	CH+ANH	84 (9)	52 (4)*	80 (12)	81 (10)	80 (15)
	CH	83 (10)	53 (5)*	78 (9)	79 (14)	79 (13)
	Control	81 (10)	72 (8)+	79 (13)	82 (11)	81 (13)
CVP (mmHg)	CH+ANH	12.2 (2.3)	11.7 (1.9)	10.8 (2.0)	11.2 (0.8)	11.8 (1.0)
	CH	12.0 (2.1)	11.5 (1.1)	11.0 (1.2)	10.8 (2.0)	12.1 (1.8)
	Control	11.8 (1.2)	11.4 (1.2)	10.9 (0.9)	11.0 (1.1)	11.5 (1.4)
HR (min^{-1})	CH+ANH	72 (8)	68 (7)	73 (10)	75 (12)	75 (14)
	CH	70 (9)	72 (9)	74 (12)	73 (13)	74 (15)
	Control	69 (8)	69 (12)	73 (9)	72 (10)	74 (12)
Pa_{O_2} (mm Hg)	CH+ANH	169 (40)	155 (41)	153 (57)	111 (31)*	90 (21)*
	CH	174 (38)	150 (36)	152 (19)	108 (31)*	95 (27)*
	Control	162 (45)	153 (37)	148 (52)	112 (42)*	91 (19)*
Pa_{CO_2} (mm Hg)	CH+ANH	34.8 (3.1)	33.5 (4.1)	34.8 (5.3)	35.9 (3.1)	35.5 (3.0)
	CH	33.7 (2.8)	32.8 (4.7)	34.1 (4.2)	34.8 (5.3)	34.9 (4.2)
	Control	35.2 (4.1)	32.5 (3.7)	34.6 (3.2)	34.3 (3.9)	35.6 (5.1)

Table 4 Duration of hypotension, anaesthetic exposure, consumption of additional anaesthetics, and recovery profile after discontinuation of anaesthetics Values are expressed as mean (SD). MAC-h, minimum alveolar concentration hours

	CH+ANH (*n*=14)	CH (*n*=14)	Control (*n*=14)
Duration of hypotension (min)	86 (20)	90 (14)	–
SNP total dose (mg)	17.4 (7.2)	16.2 (5.1)	–
Exposure to desflurane (MAC-h)	3.3 (0.4)	3.5 (0.5)	3.4 (0.4)
Consumption of anaesthetics			
Thiopental (mg)	402 (45)	391 (52)	395 (36)
Fentanyl (mg)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Rocuronium (mg)	84 (12)	86 (13)	86 (11)
Time to (min)			
Extubation	15.0 (3.2)	13.2 (2.8)	14.2 (2.4)
Opening eyes	13.2 (3.0)	11.2 (2.7)	12.4 (2.4)
Squeezing fingers	13.4 (3.1)	11.7 (2.6)	13.0 (2.6)
Stating name	18.2 (3.1)	16.6 (2.7)	17.1 (2.8)
Stating date of birth	18.5 (3.0)	17.4 (2.6)	18.0 (2.8)
PACU			
Duration of stay (min)	95.8 (17.0)	93.2 (16.5)	97.8 (21.8)
Aldrete scoring system admission	6.0 (1.0)	6.1 (0.9)	5.7 (0.8)
Aldrete scoring system discharge	7.9 (0.3)	7.8 (0.3)	7.6 (0.4)

significantly lower than in the control group (Table 2). Significantly fewer units of allogeneic PRBC were transfused in the patients receiving hypotensive anaesthesia. The amount of gelatin administered was higher in the CH+ANH group than in the two other groups (Table 2). During surgery, the haemoglobin concentration was significantly lower in the CH+ANH group than in the two other groups, but 2 and 24 h postoperatively the lowest haemoglobin values were observed in the control group (Table 3). Haemodynamic data and blood gas values showed no significant differences, except for MAP, which was significantly lower during surgery in the patients receiving hypotensive anaesthesia (Table 3). The duration of CH and the total dose of SNP administered did not differ between the CH group and the CH+ANH group (Table 4). The mean dose of desflurane and the need for additional anaesthetics were similar between the groups. The emergence time from the end of anaesthetic administration to extubation, eye opening, response to simple commands, or orientation were similar in all groups. There was no difference in the postoperative recovery profile and duration of stay in the PACU between the three groups (Table 4). None of the patients showed gross neurological deficits (e.g. stroke) or signs of myocardial ischaemia (TnT plasma levels were <0.1 μg ml^{-1} in all patients).

The baseline values of serum S-100 protein and NSE concentrations were normal in all patients and comparable between the groups. Serum S-100 protein concentrations increased significantly in all groups at the end of surgery, with a further increase 2 h postoperatively. Highest mean

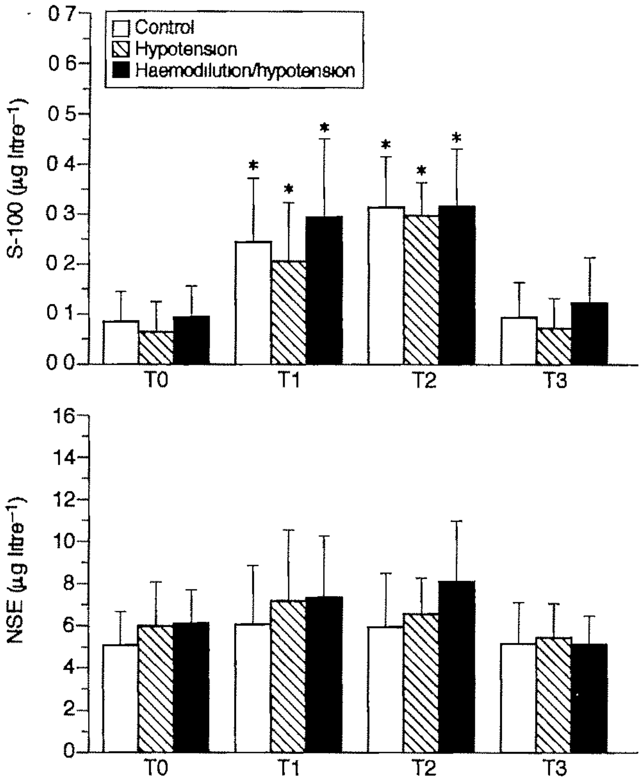

Fig 1 Concentrations of serum S-100 protein (µg litre^{-1}) and neuron-specific enolase (µg litre^{-1}) T_0=induction of anaesthesia, T_1=end of surgery; T_2=2 h postoperatively; T_3=24 h postoperatively. Values are mean (SD) *$P<0.05$, significantly different from baseline value

concentrations of this protein were detected 2 h postoperatively (CH 0.25 (0.11) µg litre^{-1}; CH+ANH 0.31 (0.12) µg litre^{-1}; control 0.31 (0.10) µg litre^{-1}). A return to baseline values was seen at the first postoperative day in all patients (Fig. 1). There were no significant changes in NSE concentrations in any group throughout the whole study period. Peak values were 7.12 (3.44) µg litre^{-1} in the CH group, 8.02 (2.92) µg litre^{-1} in the CH+ANH group, and 6.08 (2.70) µg litre^{-1} in the control group (Fig. 1). No significant correlations were found between NSE, S-100 protein, and variables of postoperative recovery.

Discussion

Both CH and ANH have demonstrated their efficacy as blood-saving techniques.[2 20] Consequently, one can speculate that the combination of CH and ANH might produce even larger blood savings.[4] One of the main findings of our study is that intraoperative blood loss and requirements for allogeneic blood transfusion were significantly reduced in patients receiving either CH or combined haemodilution and hypotension Data from our study confirmed the results of two earlier investigations comparing CH and ANH alone with a control group.[2 21] It was reported by Boldt and colleagues that blood loss and transfusion requirements were lowest in patients receiving CH, with rather disappointing results in the ANH groups. Thus, decreasing MAP seems to be an effective strategy for the reduction of intraoperative blood loss and tranfusion requirements. However, we found no further reduction in intraoperative blood loss or in requirements for allogeneic blood transfusion in patients receiving a combination of CH and ANH.

Comparison with the results of other studies is difficult, because data on the combined effects of CH and ANH are scarce. Studies dealing with this blood-saving technique are often flawed in design and execution, because they fail to compare patients who have undergone the combined technique with contemporaneous controls.[22 23] Additionally, no precise data on transfusion practice are given in most of these studies. We decided to withdraw a fixed amount of 2 units of autologous blood (1000 ml) for ANH, resulting in a post ANH haematocrit of approximately 29%. The limited effectiveness of haemodilution in this setting might be a result of the fact that the efficacy of ANH as a blood-saving strategy is proportional to the amount of blood withdrawn during the ANH procedure.[1 24] Further dilution by accepting lower limits of post ANH haematocrit would produce disproportionately larger blood savings.[24] Data on minimal acceptable limits of haemodilution are derived from several studies.[10 24 25] ANH to a target haemoglobin concentration of 7 g dl^{-1} may be performed safely in patients with intact myocardial function and without cerebrovascular disease.[10] Anaesthetized patients with known coronary and cardiac disease tolerated ANH to a target haemoglobin concentration of 10 g dl^{-1} without signs of myocardial ischaemia.[24 25] However, as there is no established safe lower limit of packed red cell volume, the blood sparing benefits of this technique must be weighed against the risk of inadequate tissue oxygenation.

Although the combination of CH and ANH was not associated with intraoperative haemodynamic instability or an increased incidence of adverse effects, the combined reduction of oxygen-carrying capacity and perfusion pressure raises concerns of hypoperfusion and ischaemic injury to the brain, heart, or other vital organs. Perioperative cerebral complications such as delayed awakening, cognitive dysfunction and stroke were associated with increased levels of brain-originated biochemical markers such as protein S-100 or neuron-specific enolase.[12 16] We found a small, but significant increase of serum S-100 protein in all our patients, irrespective of group assignment. Maximum levels occurred 2 h postoperatively, and concentrations declined to baseline values within 24 h. No previous clinical study has investigated serum levels of this specific biochemical marker for brain cell damage after CH or combined haemodilution and hypotension. The majority of studies on the release of protein S-100 was performed in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).[12] High levels of S-100 protein were recorded at the end of CPB, followed by a continuous decline to pre-CPB values within 48 h in patients who did not develop neurological signs or symptoms.[18 26] A similar pattern of release was observed in our patients. However, maximum values of S-100 protein measured in our study were only 10% of these found after CPB without complications. In patients undergoing off-pump coronary artery bypass grafting, a small but significant increase in S-100 protein levels was found during surgery.[27] Earlier studies using less sensitive analysis techniques for protein S-100 (threshold of detection: 0.2 μg litre^{-1}) found that anaesthesia alone or thoracic surgery without CPB did not initiate any release of S-100 protein into the serum.[28 29] In the present study, S-100 protein levels were analysed using a recently developed immunoluminometric assay with enhanced sensitivity, which can measure S-100 protein to 0.02 μg litre^{-1}. The conflicting results between our study and previous investigations might be explained by the fact that earlier studies using a less sensitive assay may have missed smaller increases of S-100 protein.

Both the exact mechanism of S-100 protein release after cardiac surgery with CPB and the level at which any cerebral complication can be diagnosed are unclear. An increased endothelial permeability of the blood–brain barrier because of an increased inflammatory response after CPB and neuronal cell damage secondary to diffuse microembolization were used to explain the augmented release of S-100 protein during cardiac surgery.[12 16] A more pronounced acute phase response with highly elevated cytokine inflammatory mediators such as interleukin 6 (IL-6) has also been found in patients receiving CH induced by SNP.[30] Although we did not measure biochemical markers of inflammatory response in our study, it seems possible that systemic inflammation mediated by elevated cytokine levels could have increased blood–brain barrier permeability in patients receiving hypotensive anaesthesia. This may also be attributed to the control patients, as inflammation is seen after all types of major surgery depending on the extent of tissue damage.[31] The combination of slightly increased levels of protein S-100 and normal concentrations of NSE after surgery suggests a transient disturbance of astroglial cell membrane integrity rather than irreversible neuronal ischaemia or cerebral damage. NSE, which is predominantly found in the cytoplasm of neurons, is not secreted into blood by intact neurons. After brain damage with neuronal injury this enzyme leaks from structurally damaged cells into the blood, where its levels show some correlation with the magnitude of brain cell injury.[16]

Studies on neuropsychological outcome after cardiac surgery have found a significant negative correlation between protein S-100 release, NSE concentrations and neuropsychologic performance after CBP.[32 33] By using simple measures of postoperative recovery, such as times from discontinuation of anaesthetics to extubation and orientation, or duration of stay in the PACU, we found no difference in immediate recovery profile after surgery between patients receiving the hypotensive anaesthesia regimens or control patients. Furthermore, there was no association between these variables and S-100 protein or NSE serum concentrations. This is in agreement with the results of earlier studies on the effects of postoperative cognitive dysfunction.[6 34] Eckenhoff and co-workers found no difference in perception and short-term memory in a group of young adults undergoing hypotensive anaesthesia compared with normotensive controls.[34] However, in a study by Thompson and colleagues dealing with the effects of hypotensive anaesthesia on cerebral, myocardial, renal, and hepatic function, several patients failed to complete psychomotor tests because of pain, immobility, or sedation.[6] These conflicting results might be attributed to the methods used in these studies, because a variety of different psychomotor tests, scores or scales might be applied for the assessment of functional neuropsychological outcome after major surgery. It has been pointed out by Dodds and Allison that the crucial elements in the detection of postoperative cognitive dysfunction are a sensitive test battery and taking learning effects into account.[35]

One objection to the present study may be that neither NSE nor S-100 protein has a proven relationship with brain injury, such as postoperative stroke, or neuropsychological dysfunction in well controlled outcome studies. Another limitation of this investigation is the relatively small number of healthy adult patients included. With the limited power resulting from both the small number of patients and the large number of interdependent variables measured, it would require a much larger patient population to confirm prognostic importance of NSE and S-100 protein as surrogate variables of cerebral complications outside cardiac surgery.

In conclusion, the present study demonstrated that intraoperative blood loss and requirements for allogeneic blood transfusion were significantly reduced in patients receiving CH or a combination of CH and ANH compared with control patients. No further reductions in blood loss or transfusion requirements were found by comparing patients receiving CH plus ANH with those receiving CH alone. Both CH alone and the combination of CH and ANH did not cause any serious neuronal damage or cerebral dysfunction, as levels of specific brain-originated biochemical markers and variables of immediate postoperative recovery did not show any differences between patient groups. A short-lasting increase of serum S-100 protein levels in all patients implies a transient disturbance of astroglial cell membrane integrity and an increased endothelial permeability of the blood–brain barrier in otherwise healthy men undergoing radical prostatectomy. Large studies with considerable numbers of patients must be undertaken to fully evaluate the prognostic importance and to define the role of protein S-100 and NSE as a measure of central nervous system dysfunction in the general surgical population.

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Effects of minor surgery and endotracheal intubation on postoperative breathing patterns in patients anaesthetized with isoflurane or sevoflurane

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We studied the effects of minor surgery and endotracheal intubation on postoperative breathing patterns. We measured breathing patterns and laryngeal resistance during the periods immediately before intubation (preoperative) and immediately after extubation following minor surgery (postoperative) in eight patients anaesthetized with sevoflurane and eight patients anaesthetized with isoflurane, breathing spontaneously through a laryngeal mask airway at a constant end-tidal anaesthetic concentration (1.0 MAC). In both sevoflurane-anaesthetized and isoflurane-anaesthetized patients, expiratory time was reduced and inspiratory and expiratory laryngeal resistance increased after surgery. In sevoflurane-anaesthetized patients, occlusion pressure ($P_{0.1}$) increased without changes in inspiratory time (Ti). Occlusion pressure did not change and Ti was greater in isoflurane-anaesthetized patients after surgery. Minor surgery may have a small but significant influence on breathing and increased laryngeal resistance following endotracheal intubation may modulate these changes. The difference in breathing pattern between sevoflurane and isoflurane may be a result of different responses of the central nervous system to different anaesthetics in the presence of increased laryngeal resistance.

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Breathing patterns in the immediate postoperative period can have some important clinical implications. For example, after surgery, a normal breathing pattern can be a criterion for extubation. Breathing patterns at this time are affected not only by anaesthetic and surgical factors[1–3] but also by upper airway function.[4–7] Our previous studies[8 9] showed that breathing patterns after surgery are quite different from those before surgery. However, in these studies the breathing patterns were analysed in patients with a tracheal tube, and the contribution of changes in upper airway resistance produced by endotracheal intubation was not evaluated. Furthermore, most of these patients underwent thoracotomy or laparotomy which may place a load on the respiratory system and affect breathing patterns through load compensation mechanisms.[10] The effects of endotracheal intubation on postoperative breathing patterns in patients after minor surgery have not been studied. Different volatile anaesthetics may also affect postoperative breathing patterns. The present study was performed to evaluate the breathing patterns after minor surgery in patients anaesthetized with either sevoflurane or isoflurane.

Methods

Subjects

Using sealed envelopes, 16 patients were allocated by block randomization to one of two groups of eight subjects each to receive either isoflurane (ISO group) or sevoflurane (SEVO group). All were to undergo elective minor surgery such as partial mastectomy or minor urological or ENT surgical procedures. None had clinical evidence of respiratory, cardiovascular, or neuromuscular disorders. Patient characteristics and the duration of surgery are given in Table 1. The ethics committee of the hospital approved the study, and informed consent was obtained from each subject.

Preparation of the subjects

All patients were pre-medicated with atropine 0.5 mg and midazolam 3 or 4 mg given i.m. 30 min before induction of anaesthesia. In the SEVO group, anaesthesia was induced with inhalation of sevoflurane by the single breath tech-

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Table 1 Patient details data and operation time of isoflurane and sevoflurane groups. Values are expressed as median (range)

	Isoflurane	**Sevoflurane**
Number of patients	8	8
Sex (male/female)	7/1	6/2
Age (yr)	45.0 (36–69)	47.0 (40–72)
Height (cm)	154.0 (152–173)	156.5 (145–181)
Weight (kg)	58.5 (49–76)	58.5 (48–82)
Operation time (min)	179.5 (145–227)	157.5 (65–260)

nique.[11] In the ISO group, anaesthesia was induced with inhalation of oxygen with 66% nitrous oxide followed by gradual increases in inspired isoflurane concentration to reduce breath-holding and laryngospasm during anaesthetic induction. Ventilation was then manually controlled and administration of nitrous oxide was discontinued. In both groups, after the administration of succinylcholine (1 mg kg^{-1}), a laryngoscope was used to insert a polyethylene catheter (6-Fr; Multiple Purpose Tube, Atom Medical, Tokyo, Japan) into the trachea just below the vocal cords for the measurement of subglottic pressure (P_{sg}), and a laryngeal mask airway (LMA†: size #3 or 4) was placed. Spontaneous breathing was then allowed to resume. End-tidal isoflurane and sevoflurane concentrations were monitored with a respiratory gas analyser (AS/3; Datex, Helsinki, Finland) and maintained constant (1.2% isoflurane and 1.7% sevoflurane, corresponding to 1.0 minimum alveolar anaesthetic concentration (MAC) in adult humans). Airflow ($\dot{V}$) was measured by a pneumotachograph connected to a differential pressure transducer (TP-602T; Nihon Koden, Tokyo, Japan). End-tidal carbon dioxide tension ($P\text{E}'_{CO_2}$) was measured using a side-stream capnometer (CAPNOX; Colin, Aichi, Japan). In addition to measurements of airway pressure at proximal end of LMA (P_{mask}) and P_{sg}, pressure difference between the P_{mask} and P_{sg} (P_{delta}) was directly measured with a pressure transducer (23NB005G; IC sensors, Silicon Valley, CA, USA). These data were recorded on an eight-channel thermal recorder (WS-682G; Nihon Koden, Tokyo, Japan) and stored simultaneously in a personal computer with a sampling frequency of 50 Hz by a data logging software package (LABDAT 5.2 RHT-Infodat, Montreal, Quebec, Canada) for later analysis.

Experimental procedure

When the breathing pattern was unchanged, the ventilatory variables were measured before the operation while maintaining a constant anaesthetic level (1 MAC). After the steady-state breathing measurements, the occlusion pressure ($P_{0.1}$) was obtained during an inspiratory effort against the airway occluded at end expiration for one breath. Then, vecuronium 8–10 mg, was given and a cuffed tracheal tube (ID 7.0 mm for females and 8.0 mm for males) was inserted after removal of the LMA and the polyethylene catheter. During surgery, anaesthesia was maintained with isoflurane (1–3%) or sevoflurane (1–3%) with nitrous oxide (66%), and vecuronium intermittently as necessary.

After surgery, the tracheal tube was removed and the LMA and subglottic catheter were inserted again. Residual muscle paralysis was reversed by i.v. administration of atropine 1.0 mg and neostigmine 2.0 mg, and the patients were allowed to breathe spontaneously. Adequate reversal of neuromuscular block was confirmed by the presence of stable ventilation and by observing a normal train-of-four responses to the ulnar nerve stimulation.

When the breathing pattern was stable, the same ventilatory measurements as in the period immediately before the operation were repeated while maintaining the same anaesthetic level (1 MAC).

Data analyses

Using the software (ANADAT 5.1 and 5.2; RHT-Infodat Inc., Montreal, Quebec, Canada), durations of inspiration (T_I) and expiration (T_E), duty ratio (T_I/T_{tot}: T_I divided by T_I+T_E), respiratory frequency (RR), tidal volume (V_T), and minute volume (MV) were determined from the flow signal. To analyse the respiratory waveform in detail, T_E was divided into the duration of active expiration ($T_{E\text{-active}}$; period with the presence of expiratory airflow) and the duration of end-expiratory pause ($T_{E\text{-pause}}$; period of no airflow before onset of inspiration) as evaluated by Byrick and Janssen.[12]

As the presence of LMA contributes to the P_{delta}, we estimated the resistive pressure decrease caused by the LMA. By measuring the pressure difference across the LMA passing 100% oxygen at a range of flow rates, we found that the resistance of the LMA (R_{LMA}) varies with size and flow ($\dot{V}$), and can be fitted by the following Rohrer's equations for each LMA size; LMA of #4: $R_{LMA}=0.077+0.093*\dot{V}$ (kPa $litre^{-1}$ s), LMA of #3: $R_{LMA}=0.074+0.085*\dot{V}$ (kPa $litre^{-1}$ s). Trans-laryngeal pressure (P_{larynx}) was, therefore, calculated by subtracting the $R_{LMA}*\dot{V}$ from the P_{delta} for each flow rate. We calculated laryngeal resistance (R_{larynx}) at a constant flow rate of 0.15 litre s^{-1} ($R_{larynx\text{-}0.15}$) during inspiration and expiration in addition to R_{larynx} at maximum inspiratory and expiratory flow rates ($R_{larynx\text{-}max}$).

Statistical analysis

All values are given as median (10–90th percentiles). Comparison between the pre- and postoperative variables for each group and comparison between R_{larynx} on inspiration and expiration were performed using the Wilcoxon Signed Rank test. Statistical differences were considered significant when $P<0.05$.

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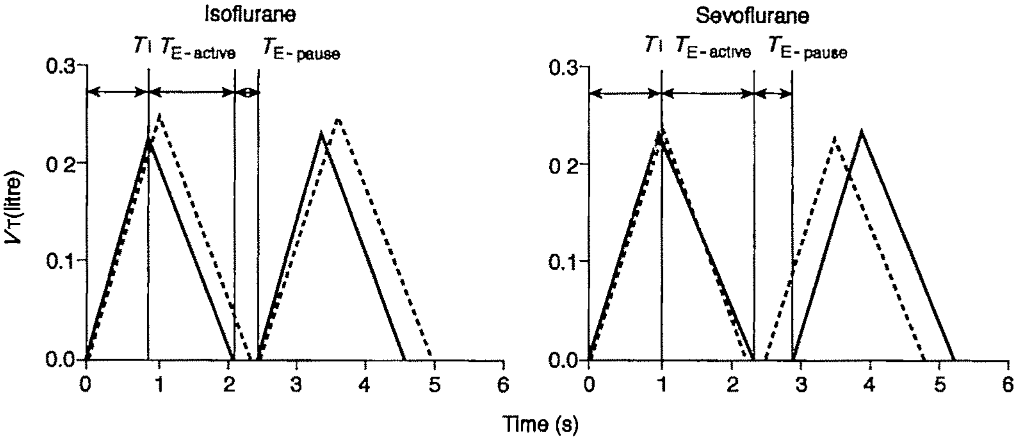

Fig 1 Volume–time relationships constructed by using median values of V_T, T_I, $T_{E\text{-active}}$, and $T_{E\text{-pause}}$ before and after surgery for each anaesthetic agent.

Results

The two patient groups were similar with respect to physical characteristics (Table 1). The duration and the types of surgery did not differ between the groups.

Breathing patterns

Ventilatory variables and the values of PE'_{CO_2} obtained from each group before and after operation are shown in Table 2. In the ISO group, T_I was longer (P=0.008) and T_E shorter (P=0.016) after surgery while *RR* did not change. In the SEVO group, T_I did not change after surgery while T_E was significantly less than before surgery (P=0.008), resulting in a slight, but significant increase in *RR* (P=0.016). In addition to these changes, $P_{0.1}$ significantly increased after the surgery in SEVO group (P=0.016). In both groups, T_E was less because $T_{E\text{-pause}}$ was less (P=0.008) (Fig. 1). T_I/T_{tot} increased after surgery in both groups (P=0.008). No difference was observed in V_T, *MV*, and PE'_{CO_2} before and after the surgery.

Laryngeal airway resistances (R_{larynx})

Figure 2 shows an example of P_{larynx}–$\dot{V}$ relationships before and after surgery in one subject of the ISO group. The P_{larynx}–$\dot{V}$ relationships were curvilinear both on inspiration and expiration, and a large amount of hysteresis was present particularly on inspiration. The slope of the postoperative P_{larynx}–$\dot{V}$ curve, which represents translaryngeal airway resistance, was always greater than that of preoperative curve both on inspiration and expiration.

Changes of R_{larynx} before and after surgery for each group are given in Table 3. Both $R_{larynx\text{-}0.15}$ and $R_{larynx\text{-max}}$ were significantly greater after surgery than before surgery both on inspiration (P=0.016, P=0.016 ISO group and P=0.016, P=0.008 SEVO group, respectively) and expiration (P=0.023, P=0.039 ISO group and P=0.023, P=0.039 SEVO group, respectively). There were no significant differences in the values of $R_{larynx\text{-}0.15}$ between inspiration and expiration in both the ISO and SEVO groups.

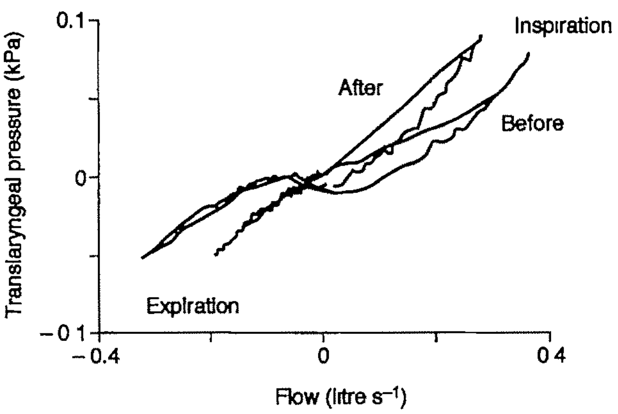

Fig 2 Translaryngeal pressure–flow relationship in a subject anaesthetized with isoflurane. Note that laryngeal airway resistance was always higher after surgery than before surgery (before=before surgery; after=after surgery).

Discussion

The major findings of this study were as follows: (1) a significant shortening of T_E and an increase in T_I/T_{tot} were observed after surgery both during isoflurane anaesthesia and during sevoflurane anaesthesia; (2) T_I increased only during isoflurane anaesthesia; (3) $P_{0.1}$ increased during sevoflurane anaesthesia but it did not change during isoflurane anaesthesia after surgery; and (4) R_{larynx} significantly increased both during isoflurane anaesthesia and during sevoflurane anaesthesia. Thus, the results indicated that minor surgery with endotracheal intubation affects breathing patterns in postoperative period, and that sevoflurane and isoflurane had different effects.

Postoperative breathing pattern

Breathing abnormality, such as rapid shallow breathing with increase in central respiratory drive, has been reported to occur after upper abdominal and thoracic surgery.[2 3 9 13 14] Postoperative pain relief did not normalize the breathing pattern after lower abdominal surgery.[15] Tulla and colleagues found that minor surgery had a minimal effect on the breathing pattern.[16] Postoperative breathing pattern may thus depend on the magnitude of the surgical stress, unrelated to pain. We observed no significant changes in $V\text{T}$, MV, and $P\text{E}'_{CO_2}$ in our patients, but, this does not necessarily mean that minor surgery does not affect the breathing pattern at all. Detailed analysis of breathing pattern from a consistent shortening of $T\text{E}$ and increase in $T\text{I}/T_{tot}$ after surgery in both the ISO and SEVO groups. The differences in $T\text{I}$ and $P_{0.1}$ suggest that minor surgery may have different effects on respiratory control, depending on the different anaesthetic agents. The effects we found could also be caused by a time effect as the design of our study does not allow us to be sure that the changes found were related specifically to the effects of minor surgery. The respiratory depression caused by volatile anaesthetics decreases with time despite the same end-tidal concentration of volatile anaesthetics, and the degree of recovery from respiratory depression is different between different volatile anaesthetics.[17]

There was a considerable difference in the values of $P_{0.1}$ obtained before the surgery between the ISO and SEVO groups. Although the underlying mechanisms are unclear, the difference might be primarily a result of the different effects of the two agents on the central respiratory neural network, secondary to the difference in the shape of occlusion pressure waveform between the two groups. Thus, we should be cautious about comparing the $P_{0.1}$ values of the two groups.

Role of the larynx

We examined the breathing pattern without bypassing the larynx, which is an internal variable resistance that may control respiratory timing.[5] Respiratory timing is determined by interaction between central modulation and peripheral mechanics, and postoperative changes in respiratory timing may be affected by the laryngeal airflow regulation. Kuna, Insalaco and Woodson[18] measured laryngeal adductor muscle activity in awake and sleeping human adults, and demonstrated that while awake, the level of phasic expiratory activity was directly related to $T\text{E}$ and expiratory R_{larynx}, but the activity was absent in NREM sleep. We know of no study on laryngeal modulation of the respiratory timing in anaesthetized humans. Although we did not measure laryngeal muscle action, we found no

Table 2 Ventilatory variables and $P\text{E}'_{CO_2}$ of each group before and after surgery. $V\text{T}$=tidal volume, $T\text{I}$=duration of inspiration; $T\text{E}$=duration of expiration, $T_{\text{E-active}}$=duration of active expiration; $T_{\text{E-pause}}$=duration of end-expiratory pause, T_{tot}=respiratory cycle time, $T\text{I}/T_{tot}$=duty ratio, RR=respiratory frequency; MV=minute volume, $P_{0.1}$=inspiratory occlusion pressure at 0.1 s; $P\text{E}'_{CO_2}$=end-tidal carbon dioxide tension. Values are expressed as median (10–90%) *$P<0.05$ and **$P<0.01$, respectively, *vs* before surgery

	Isoflurane		**Sevoflurane**	
	Before	**After**	**Before**	**After**
$V\text{T}$ (litre)	0.23 (0.18–0.42)	0.23 (0.18–0.35)	0.23 (0.21–0.37)	0.22 (0.17–0.35)
$T\text{I}$ (s)	0.87 (0.69–1.19)	1.05 (0.80–1.30)**	0.99 (0.81–1.17)	1.03 (0.81–1.20)
$T\text{E}$ (s)	1.70 (1.48–2.36)	1.60 (1.18–2.01)*	1.92 (1.56–3.36)	1.48 (1.31–2.08)**
$T_{\text{E-active}}$ (s)	1.23 (1.21–1.45)	1.29 (1.03–1.61)	1.34 (1.16–1.48)	1.22 (1.11–1.40)
$T_{\text{E-pause}}$ (s)	0.41 (0.28–0.92)	0.26 (0.15–0.41)**	0.58 (0.27–1.96)	0.26 (0.18–0.75)**
$T\text{I}/T_{tot}$	0.35 (0.27–0.42)	0.39 (0.34–0.51)**	0.34 (0.26–0.37)	0.40 (0.34–0.43)**
RR (breath min^{-1})	23.0 (18.1–26.1)	23.1 (19.4–29.2)	21.2 (13.6–24.9)	24.3 (18.7–28.3)*
MV (litre min^{-1})	5.01 (3.78–10.65)	4.97 (3.95–9.38)	4.97 (3.63–7.03)	5.69 (3.60–8.33)
$P_{0.1}$ (kPa)	0.17 (0.10–0.26)	0.20 (0.10–0.29)	0.09 (0.07–0.23)	0.24 (0.08–0.36)*
$P\text{E}'_{CO_2}$ (kPa)	5.33 (5.15–6.09)	5.47 (5.07–6.13)	5.60 (5.07–6.13)	5.67 (4.69–6.28)

Table 3 Laryngeal airway resistances (R_{larynx}) of each group before and after surgery. Values are expressed as median (CI 10–90%) (kPa litre^{-1} s) *$P<0.05$ and **$P<0.01$, respectively, *vs* before surgery

	Isoflurane		**Sevoflurane**	
	Before	**After**	**Before**	**After**
R_{larynx} at maximum inspiratory flow	0.18 (0.04–0.22)	0.30 (0.22–0.75)*	0.16 (0.11–0.27)	0.49 (0.11–0.98)*
R_{larynx} at maximum expiratory flow	0.17 (0.05–0.24)	0.31 (0.17–0.64)*	0.17 (0.10–0.30)	0.44 (0.11–1.10)*
R_{larynx} at a flow of 0.15 litre s^{-1}				
On inspiration	0.16 (0.05–0.20)	0.22 (0.16–0.48)*	0.11 (0.05–0.22)	0.36 (0.09–0.54)**
On expiration	0.13 (0.04–0.21)	0.24 (0.13–0.45)*	0.15 (0.07–0.21)	0.36 (0.08–0.65)*

difference in resistance between inspiration and expiration, unlike the awake condition.[19] Laryngeal regulation of respiratory airflow under general anaesthesia is probably less than in conscious state and the larynx may not have had an important role in the modulation of respiratory timing in our quietly breathing anaesthetized subjects. We did find that laryngeal resistance had increased after the surgery, probably from changes such as laryngeal swelling produced by the endotracheal intubation.

The influence of increased laryngeal resistance on the postoperative breathing pattern

It is reasonable to consider that an increase in laryngeal resistance could affect breathing pattern after minor surgery. Flow limitation by increased laryngeal resistance could prolong both T_I and T_E, reduce *RR*, and decrease *MV*. However, we did not find any reduction of *RR*, and *MV* was well preserved. Compensatory mechanisms may be active. Although T_I increased in the ISO group, this prolongation did not accompany changes in $P_{0.1}$. This could mainain V_T in the face of increased laryngeal resistance. In contrast, $P_{0.1}$ increased without changes in T_I in SEVO group, suggesting that augmentation of neural drive has occurred. The compensatory mechanisms in response to a small increase in laryngeal inspiratory resistance during isoflurane anaesthesia seem to differ from those during sevoflurane anaesthesia, although we have no explanation for the difference between the two anaesthetic agents.

T_I/T_{tot} consistently increased in both the SEVO and ISO groups after minor surgery in this study and this increase was mainly a result of significant shortening of T_E. The increase in T_I/T_{tot} was ascribed from shortening of $T_{E\text{-pause}}$ and that the duration of active expiration did not alter after the surgery. It is likely that these changes are caused by the effects of minor surgery on respiratory control and for the shortneing of $T_{E\text{-pause}}$ may be compensation for the increase in expiratory flow resistance.

Minor surgery changes breathing pattern, affecting respiratory timing. This change in breathing pattern may result from an increase in laryngeal resistance caused by endotracheal intubation. There was also a slight difference in postoperative breathing pattern between sevoflurane and isoflurane, presumably because the central nervous system has different responses to different anaesthetics.

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Use of multi-plane transoesophageal echocardiography in visualization of the main hepatic veins and acquisition of Doppler sonography curves. Comparison with the transabdominal approach

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The role of multi-plane transoesophageal echocardiography (TOE) in the visualization of the three main hepatic veins and acquisition of Doppler sonography curves has not been established. We have studied this diagnostic option of TOE in 34 patients during general anaesthesia. The findings were compared with the results of conventional transabdominal sonography (TAS). Using TOE, each of the three main hepatic veins could be visualized in all patients. In contrast, TAS allowed adequate two-dimensional visualization of the right, middle, and left hepatic vein in only 97%, 85%, and 61% of the patients, respectively. Adequate Doppler tracings of the right and middle hepatic vein could be obtained in 100% and 97% of the patients by TOE and in 91% and 50% of the patients by TAS. Doppler tracings of the left hepatic vein could only be acquired in 18% of the patients by TOE, but in 47% of the patients by TAS. As blood flow may be calculated from the diameter of the vessel, velocity time integral of the Doppler curve and heart rate, TOE may provide an interesting non-invasive tool to monitor blood flow in the right and middle hepatic vein.

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Assessment of hepatic and splanchnic perfusion is of scientific and clinical interest. Transabdominal Doppler ultrasound has been proposed as a non-invasive technique to assess hepatic vein flow,[1–3] but this approach is associated with several limitations. First, the intra-operative application of transabdominal ultrasound during abdominal or thoracic surgery is not feasible because of interference with the surgical field. Second, in many mechanically ventilated patients, especially after intra-abdominal surgical procedures, trans-abdominal application of ultrasound does not deliver images of satisfactory quality. The possibility of assessing hepatic vein flow using transoesophageal echocardiography (TOE) was first mentioned by Pinto and coworkers in 1991.[4] This group was unable to visualize and describe in detail the anatomy of the different hepatic veins using their monoplane transoesophageal echoprobe. Multiplane transoesophageal echoprobes have since become widely available in many hospitals. Therefore, the main objective of the present study was to evaluate the use of multi-plane TOE in the visualization of the main hepatic veins and acquisition of analysable Doppler sonography curves. The second objective was to compare the transoesophageal technique with the conventional transabdominal approach.

Methods

Patients

We studied 34 patients undergoing abdominal surgery under general anaesthesia and mechanical ventilation. The study was approved by the ethics committee of the University of Ulm. Written informed consent was obtained from all patients before inclusion in the study.

All patients were without known cardiovascular disease and were demonstrated to be in sinus rhythm by an electrocardiogram. According to the ASA criteria, 14 patients were classified as group I, 14 patients as group II and six patients as group III. The mean age was 46.5 and ranged from 23 to 80 yr. After induction of general anaesthesia and endotracheal intubation, patients' lungs

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were mechanically ventilated ($F\text{I}_{\text{O}_2}$ 0.3–0.4; PEEP 5 cm H_2O) with a tidal volume of 8–10 ml kg^{-1} at a ventilatory frequency of 8–10 breaths min^{-1} adjusted to maintain end-tidal $P\text{CO}_2$ between 35 and 40 mm Hg.

Sonography and Doppler sonography measurements

Transabdominal approach

After induction of general anaesthesia, transabdominal recordings of the right, middle, and left hepatic vein were obtained using a Hewlett Packard echocardiograph (Sonos 5500, Hewlett-Packard Inc., Andover, MA, USA) with a 2.5 MHz transducer. For visualization of the right hepatic vein a lateral thoracic approach was used, for visualization of the middle and left hepatic vein a subxiphoidal or right subcostal view was chosen. Two-dimensional pictures of the hepatic veins were obtained in the B-mode. Subsequently blood-flow velocities in each hepatic vein were acquired by use of pulsed Doppler (PW)-mode. The Doppler sample-volume was placed in the centre of the vessel, 1–3 cm from its junction with the inferior vena cava.

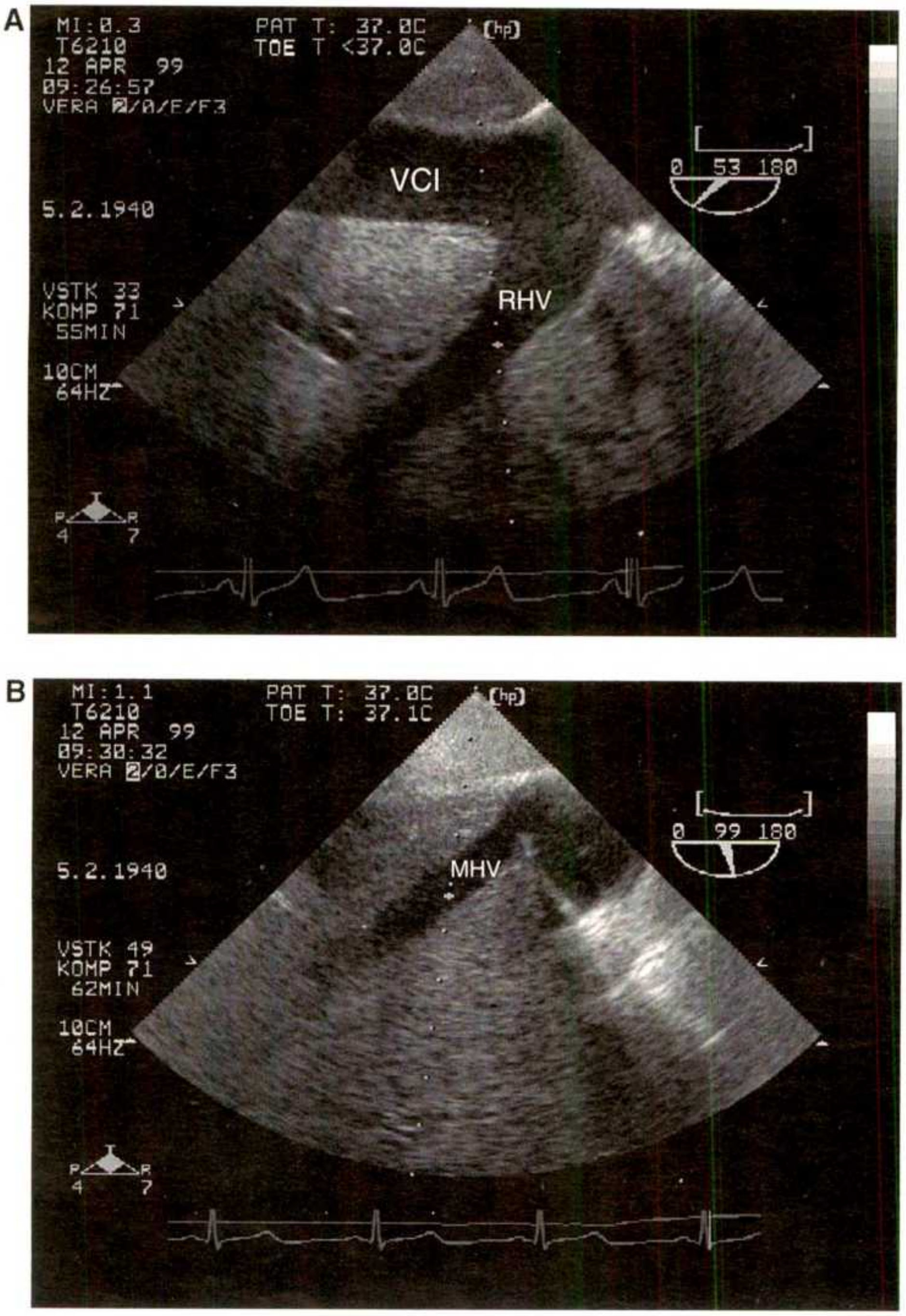

Fig 1

Correction of the angle between the Doppler beam and long axis of the hepatic vein was performed for each Doppler measurement using the software of the echocardiograph. Two-dimensional pictures and Doppler signals were obtained at the end of expiration along with lead II of the ECG and stored on a magneto-optical disc. To verify the end of expiration, an external breathing circuit pressure gauge (Fa. Draeger, Lübeck, Germany) was connected to the echocardiograph to visualize the airway pressure on the screen. Analysis of the echo data was performed off line using the software of the echocardiograph. Two-dimensional images and flow velocity curves were judged adequate for analysis only when clear signals were depicted at the end of expiration.

Transoesophageal approach

After acquisition of the transabdominal views a 5.0 MHz multi-plane transoesophageal probe (Omniplane I, Hewlett-Packard Inc., Andover, MA, USA) was inserted and connected to the same echocardiograph. To visualize the hepatic veins the tip of the probe was advanced into the antrum of the stomach and flexed anteriorly. By rotating the probe clockwise and adjusting the imaging angle of the transducer array to 40–80° a saggital view of the inferior vena cava and the right hepatic vein was obtained. By rotating the probe counter-clockwise and increasing the angle of the transducer array to 50–90° the middle hepatic vein was visualized, by further counter-clockwise rotation of the probe and increasing the angle of the transducer array to 80–130° an image of the left hepatic vein was acquired. When feasible, a two-dimensional picture of each hepatic vein was acquired in the B-mode and a Doppler sonography curve was obtained in the PW-mode. As described for the transabdominal approach the images were recorded along with an ECG-lead at the end of expiration and stored on a magneto-optical disc.

Analysis of the Doppler sonography curve

Hepatic venous flow during a cardiac cycle can be divided into a systolic forward flow, diastolic forward flow, and a diastolic reversed flow induced by atrial contraction.[2–4] Sometimes, also, a small systolic reversed flow can be identified. Peak flow velocities and velocity time integrals of the four phases were measured by manual planimetry using the integrated software of the echocardiograph. The velocity time integral is the calculated area under the Doppler curve over a specified period.[5] The velocity time integral represents the distance the blood travels during the specified period. The total velocity time integral during one cardiac cycle was determined by addition (forward flow) and subtraction (reversed flow), respectively, of the four single velocity time integrals.

Calculation of the blood flow in the hepatic veins

Blood flow in a distinct hepatic vein was calculated using the formula: Blood flow = $\mathrm{VTI} \times \pi\ (D/2)^2 \times \mathrm{HR}$ (VTI: total velocity time integral of one cardiac cycle, $\pi\ (D/2)^2$ cross-sectional area of the vessel, HR: heart rate).[6 7] The diameter (D) of the vessel was determined at the same part of the vessel, where the PW-Doppler sample volume was placed.

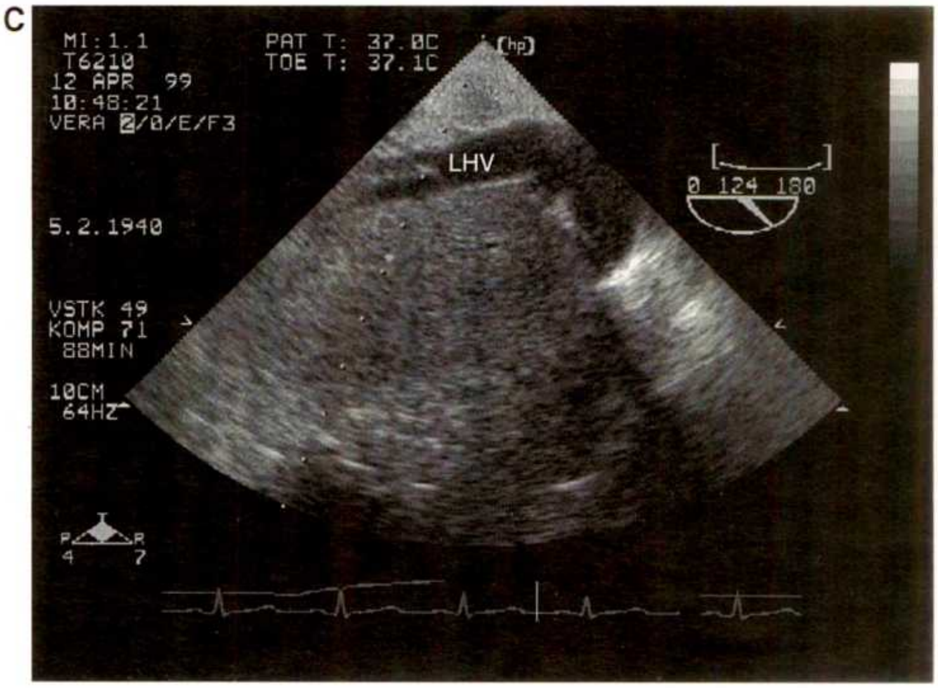

Fig 1 (A) Two-dimensional picture of inferior vena cava (VCI) and right hepatic vein (RHV) obtained by the transoesophgeal approach (multi-plane angle 53°). (B). Two-dimensional picture of middle hepatic vein (MHV) (multi-plane angle 99°). (C) Two-dimensional picture of left hepatic vein (LHV) (multi-plane angle 124°).

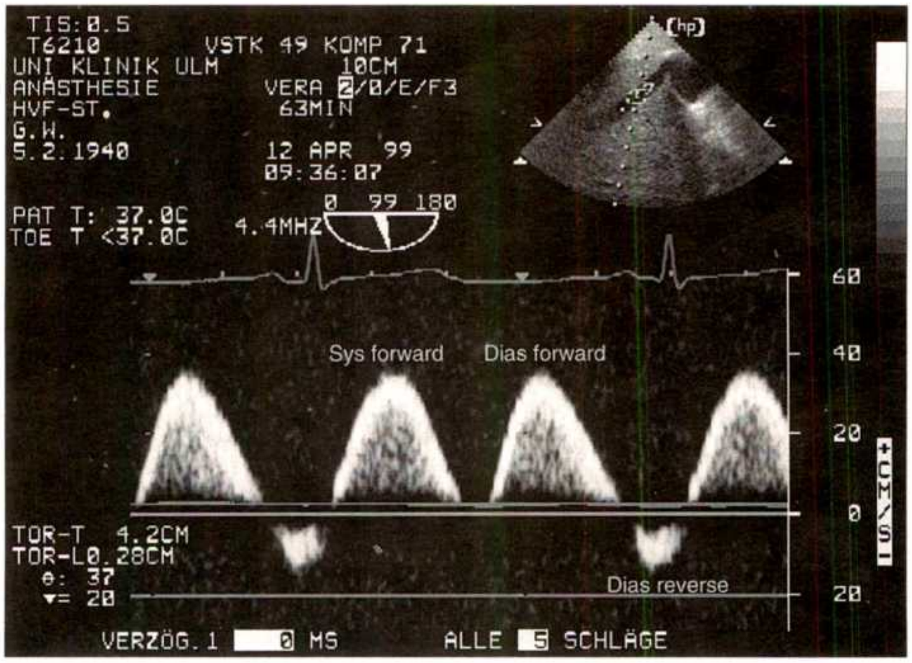

Fig 2 Characteristic Doppler sonography curve of middle hepatic vein obtained by the transoesophageal approach. The flow pattern shows a systolic forward flow, a diastolic forward flow and a small diastolic reversed flow, induced by atrial contraction.

Table 1 Percentage of patients revealing a systolic reverse flow and diastolic reverse flow in the main hepatic veins (HV). Results of the transoesophageal (TOE) and transabdominal (TA) approach

	Systolic reverse flow		Diastolic reverse flow	
	TOE	TA	TOE	TA
Right HV	15% (5/34)	3% (1/31)	53% (18/34)	29% (9/31)
Middle HV	6% (2/33)	0% (0/17)	58% (19/33)	17% (3/17)
Left HV	16% (1/6)	12% (2/17)	83% (5/6)	35% (6/17)

Heart rate was derived from the ECG recorded together with the Doppler images.

Statistical analysis

Discrete variables were described as absolute and relative frequencies. All continuous variables were presented as median (range). Differences between transthoracic and transoesophageal data were compared using the Mann–Whitney Rank Sum Test. Statistical significance was assumed when the *P*-value was <0.05.

Results

Visualization of the main hepatic veins

Using TOE adequate two-dimensional images of the right, middle, and left hepatic vein were obtained in all patients. Typical pictures of the right, middle, and left hepatic veins obtained by TOE are given in Figure 1A–C. For optimal visualization of the right, middle, and left hepatic vein, the imaging angle of the transducer array was rotated to median (range) 66° (38–86°), 75° (49–99°), and 108° (73–129°), respectively.

Using the transabdominal approach, adequate two-dimensional visualization of the right, middle, and left hepatic vein was possible in 97% (33/34), 85% (29/34), and 61% (21/34) of the patients, respectively. Interestingly, one patient revealed two right hepatic veins entering separately into the inferior vena cava. This was not detected by the transabdominal approach.

Acquisition of adequate Doppler sonography curves of the main hepatic veins

Using TOE adequate Doppler tracings of the right hepatic vein were obtained in 100% (34/34) and of the middle hepatic vein in 97% (33/34) of the patients. A characteristic Doppler sonography curve of the middle hepatic vein obtained by TOE is depicted in Figure 2. In most patients the angle between the left hepatic vein and the Doppler beam was greater than 60° (see Fig. 1C). Therefore, adequate Doppler tracings of the left hepatic vein could only be acquired in 18% (6/34) of the patients by the transoesophageal approach.

Transabdominal sonography (TAS) allowed acquisition of adequate Doppler tracings of the right hepatic vein in 91% (31/34) and of the middle hepatic vein in only 50% (17/34) of the patients. Doppler tracings of the left hepatic vein were obtained in 47% (16/34) of the patients, but most

Table 2 Peak velocities and velocity time integrals of the different phases of hepatic vein flow obtained by the transoesophageal (TOE) and transabdominal (TA) approach. Sys_f, systolic forward flow; $Dias_f$, diastolic forward flow, $Dias_r$, diastolic reversed flow. Data given as median Comparison between the transoesophageal and transabdominal value· *$P<0.05$

		Right HV		**Middle HV**		**Left HV**	
		TOE (n=34)	**TA (n=31)**	**TOE (n=33)**	**TA (n=17)**	**TOE (n=6)**	**TA (n=17)**
Sys_f	Peak (cm s^{-1})	16.7	17.9	16.1	19.7	15.2	17.1
	VTI (cm)	4.2	3.7	4.4	4.2	3.4	3.3
$Dias_f$	Peak (cm s^{-1})	15.9	17.6	18.3	20.1	14.2	19.7
	VTI (cm)	4.4	4.4	4.6	4.4	3.4	4.2
$Dias_r$	Peak (cm s^{-1})	5.1	0	6.4	0	9.6	0
	VTI (cm)	0.4	0	0.6	0*	0.96	0

Table 3 Calculated blood flow in the main hepatic veins assessed by the transoesophageal (TOE) and transabdominal (TA) approach Data given as median (range). n=number of patients

	Right HV	**Middle HV**	**Left HV**
Blood flow (ml min^{-1}) TOE	523 (172–1886) n=34	232 (83–818) n=33	113 (66–174) n=6
Blood flow (ml min^{-1}) TA	456 (94–1841) n=31	153 (69–540) n=17	176 (73–456) n=16

Doppler tracings were superimposed by artefacts probably caused by heart motion.

Comparison of the Doppler curves obtained by the transoesophageal and transabdominal approach

In all patients a diastolic forward flow and in about 90% of the patients a systolic forward flow was observed in the three main hepatic veins using both techniques. As demonstrated in Table 1 a systolic and diastolic reverse flow was detected by TOE in more patients than with the transabdominal approach.

The peak velocities and velocity time integrals of the different phases of hepatic vein flow are presented in Table 2. Comparison of the transoesophageal and transabdominal acquired values revealed a significant difference ($P<0.05$) only for the velocity time integral of the diastolic reverse flow in the middle hepatic vein.

Calculated blood flow in the different hepatic veins

The calculated blood flows in the different hepatic veins are presented in Table 3. Statistical comparison did not reveal a significant difference between blood flow values obtained by TOE and TAS.

Discussion

This is the first study to describe in detail the visualization of the different hepatic veins by using multi-plane TOE. The main result of the present study is that TOE allows two-dimensional visualization of the three main hepatic veins in all patients. In comparison with the transabdominal technique, the transoesophageal approach enables the investigator to visualize the different hepatic veins in more patients and with better quality. The explanation for this observation is the anatomical proximity of the distal oesophagus and the antrum to the hilus of the liver.

Furthermore, good quality Doppler curves of the right and middle hepatic vein can be obtained by TOE. Almost all patients revealed adequate Doppler curves of the right (100% of the patients) and middle hepatic vein (97% of the patients) by the transoesophageal technique. Using the transabdominal approach, adequate Doppler curves of the right and middle hepatic vein could only be obtained in 91% and 50% of the patients. For the middle hepatic vein, this finding is in accordance with the results of Appleton and colleagues[3] and Klein and colleagues[8] who, using the transabdominal approach, obtained adequate Doppler tracings of the middle hepatic vein in 30% and 46% of healthy subjects, respectively. These groups did not assess hepatic vein flow in the right hepatic vein.

Using TOE assessment of hepatic vein flow in the left hepatic vein is not possible in most patients, as the angle of insonation is greater than 60°. However, the transabdominal technique allowed acquisition of Doppler curves of the left hepatic vein in only 47% of the patients and the majority of the Doppler curves revealed artefacts probably caused by heart motion, which is transmitted to the left side of the liver. Therefore, the left hepatic vein is of limited value for blood flow analysis or calculations.

TOE was superior to TAS for detection and visualization of systolic and diastolic reverse flow. We observed this phenomenon more often using TOE in comparison with the transabdominal approach. This observation suggests that, because of the anatomical proximity, the transoesophageal technique is more sensitive to detect low blood-flow velocities or small changes of blood flow in the hepatic veins. Analysis of reverse flow in the hepatic veins is interesting in the context of different diseases of the right heart. First, the extent of the diastolic reverse flow is associated with the contractility of the right atrium.[9 10] In patients with atrial fibrillation or atrial electromechanical dissociation, as seen after cardioversion of atrial fibrillation or cardiopulmonary bypass, a diastolic reverse flow will not be present. Second, analysis of hepatic venous reverse flow allows supplementary quantification of tricuspid regurgitation.[9 11 12] In severe tricuspid regurgitation, an appreciable holosystolic reverse flow appears and all forward flow occurs during diastole. Patients with lesser degrees of tricuspid regurgitation have little or no systolic reverse flow. Third, right ventricular diastolic dysfunction is associated with characteristic changes in hepatic venous flow pattern.[9 13 14] Patients with a decreased right ventricular compliance reveal an increase in diastolic reverse flow. In analogy to pulmonary venous reverse flow an increase in the diastolic reverse flow might be useful to distinguish 'pseudonormal' right ventricular filling in patients with impaired relaxation from normal right ventricular filling.[15 16]

In comparison with data recently published by Klein and colleagues[8] for the middle hepatic vein, we observed a similar mean value for the diastolic peak velocity (23.3 (12.6) *vs* 23.0 (8.0) cm s^{-1}), but a markedly lower value for the systolic peak velocity (16.8 (9.5) *vs* 38.0 (11.0) cm s^{-1}) by the transabdominal approach. One explanation for this difference is that we used patients who were under general anaesthesia and mechanical ventilation, whereas Klein and co-workers investigated awake spontaneously breathing patients. This is supported by the studies of Pinto and colleagues[4] who observed lower peak velocities of the systolic flow under general anaesthesia and mechanical ventilation in comparison with values obtained preoperatively under spontaneous breathing.

Two previous studies did use TOE in an attempt to assess hepatic venous blood flow.[17 18] Gardebäck and co-workers, using a biplane TOE probe, were not able to visualize the different hepatic veins in a long axis view and they did not describe which of the three hepatic veins was chosen for blood flow calculations.[17] Recently, Sato and colleagues, for the first time, used multi-plane TOE for determination of hepatic blood flow in the middle hepatic vein during laparoscopic surgery.[18] The present study is the first attempt to assess blood flow in the different hepatic veins by using multi-plane TOE.

The method of calculating blood flow by Doppler sonography contains several limitations. The formula used for Doppler sonographic calculation of blood flow is based on the mean velocity within the vessel and the cross-sectional area of the vessel.[6] Inaccuracy in determining the diameter of the vessel by the use of ultrasound will produce a large error because the errors will be multiplied in determining the area. This method assumes that the velocity profile within the vessel is consistent.[6 7] This assumption seems to be accurate for the velocity profile within valve orifices, as several studies have demonstrated an excellent agreement between echocardiographic and invasive determination of cardiac output.[19 20] Within small vessels the velocity profile is known to be more parabolic. Measuring the maximal velocity within such a vessel will result in an overestimation of the true blood flow. A specific limitation of the transoesophageal approach is that assessment of total hepatic vein flow is not possible, because blood flow in the left hepatic vein cannot be determined in most patients. Nevertheless, multi-plane TOE might be an interesting tool to monitor changes in hepatic and splanchnic perfusion, in particular during therapeutic interventions in intensive care patients. Recently, we have demonstrated in a pig model that TOE provides a reasonable method to detect changes in hepatic vein flow.[21] Experimental studies in humans are necessary to test this diagnostic option of TOE against the standard methods, for example indocyanine green-clearance.[22]

Hepatic vein flow is determined by a series of different factors. Both elevated intra-thoracic pressure induced by PEEP ventilation and elevated intra-abdominal pressure induced by pneumoperitoneum during laparoscopic surgery may decrease liver and splanchnic perfusion.[23 24] Also, an increase in central venous pressure as a consequence of right heart failure may reduce hepatic blood flow.[25] In particular, in septic patients different catecholamines have been shown to have different effects on hepatic and splanchnic perfusion.[26 27]

Accurate assessment of hepatic vein flow patterns is not limited to questions of hepatic and splanchnic perfusion. Analysis of hepatic vein flow patterns may provide interesting insights into right heart dynamics intra-operatively or in critically ill patients.[10 28] Our results suggest that the transoesophageal technique seems to be a superior technique in the analysis of right atrial and ventricular function in most patients. Furthermore, determination of hepatic vein flow by Doppler sonography has been demonstrated to be helpful in diagnosing acute rejection after liver transplantation.[29] Intra-operative determination of hepatic vein flow during liver resection and transplantation has been shown to be a helpful tool to support the surgical procedure.[30] Recently, Nagueh and co-workers have demonstrated, that analysis of hepatic vein flow pattern allows reliable estimation of central venous pressure.[31]

Although TOE is regarded as a safe method and reports of serious complications are rare, it may cause serious injuries such as hypopharyngeal and oesophageal perforation or oesophageal bleeding as a result of insertion and use of TOE probes.[32 34] Especially in patients with portal hypertension and oesophageal varices, the risk of bleeding complications is increased. Therefore, the demonstrated advantages of TOE have to be balanced against the potential for causing inadvertent morbidity, which is significantly higher than with TAS.

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Comparative efficacy and safety of remifentanil and fentanyl in 'fast track' coronary artery bypass graft surgery: a randomized, double-blind study

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This multi-centre, parallel group, randomized, double-blind study compared the efficacy and safety of high-dose remifentanil administered by continuous infusion with an intermittent bolus fentanyl regimen, when given in combination with propofol for general anaesthesia in 321 patients undergoing elective coronary artery bypass graft surgery. A significantly lower proportion of the patients who received remifentanil had responses to maximal sternal spread (the primary efficacy endpoint) compared with those who received fentanyl (11% vs 52%; $P<0.001$). More patients who received remifentanil responded to tracheal intubation compared with those who received fentanyl (24% vs 9%; $P<0.001$). However, fewer patients who received remifentanil responded to sternal skin incision (11% vs 36%; $P<0.001$) and sternotomy (14% vs 60%; $P<0.001$). Median time to extubation was longer in the subjects who received remifentanil than for those who received fentanyl (5.1 vs 4.2 h; $P=0.006$). There were no statistically significant differences between the two groups in the times for transfer from intensive care unit or hospital discharge but time to extubation was significantly longer in the remifentanil group. Overall, the incidence of adverse events was similar but greater in the remifentanil group with respect to shivering ($P<0.049$) and hypertension ($P<0.001$). Significantly more drug-related adverse events were reported in the remifentanil group ($P=0.016$) There were no drug-related adverse cardiac outcomes and no deaths from cardiac causes before hospital discharge in either treatment group.

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Cardiovascular stability is an essential prerequisite for cardiac anaesthesia, where myocardial protection is vital in patients who already have compromised cardiovascular function. Traditionally, profound intraoperative analgesia has been provided by using high doses of opioids to suppress hormonal and metabolic stress responses to surgical stimuli. This regimen resulted in improved morbidity and mortality after cardiac surgery.[1 2] However, high doses or prolonged administration of conventional opioids can result in their accumulation, leading to postoperative respiratory depression and prolonged stay in the intensive care unit (ICU).[2] In many centres, economic considerations have resulted in the adoption of cardiac anaesthesia regimens using low- to medium-dose opioids administered intermittently aiming to reduce time to extubation and postoperative ICU and hospital stay. Such regimens have been shown to allow reductions in extubation times and in hospital stay[3–5] and recent studies have indicated that there is no adverse influence on the incidence of postoperative sequelae in low-risk cardiac patients.[6 7] However, there is

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evidence that the level of intraoperative analgesia (hypertension and tachycardia) may influence the risk of postoperative myocardial infarction in all patients undergoing cardiac surgery.[2 8]

Remifentanil hydrochloride is a potent μ-opioid receptor agonist characterized by a predictable rapid offset of action as a result of its metabolism by non-specific esterases in blood and other tissues. The aim of this study was to compare the efficacy and safety of remifentanil using a total i.v. anaesthesia technique in combination with propofol (high-dose opioid regimen) with a commonly used low/medium-dose fentanyl plus propofol regimen in patients undergoing elective coronary artery bypass graft (CABG) surgery who were potentially eligible for early extubation/ICU discharge.

Patients and methods

This prospective, randomized, double-blind, parallel group study was conducted at 23 centres in 10 countries. Local Ethics Committee or Review Board approval was obtained at each study centre and informed written consent was obtained from each patient. Patients aged ≥18 yr with ASA status II–IV and ejection fraction >0.3, undergoing elective CABG surgery were randomized to receive either remifentanil or fentanyl as part of a total i.v. anaesthesia technique with propofol. A total of 321 patients were recruited, of whom 24 were treated on an open label basis as 'pilot' patients and 297 were randomized to treatment.

All patients included in the study were potentially eligible for early extubation/ICU discharge. Patients with severely impaired left ventricular function (ejection fraction <0.3), significant arrhythmias, evidence of severe congestive heart failure, intra-aortic balloon assist device preoperatively, or severely impaired major organ function were excluded. Patients were also excluded from the study if they required preoperative inotropic support, or were undergoing CABG with simultaneous valve repair/replacement, or any other combined surgical procedure. Other exclusion criteria were body weight over 50% above ideal body weight, hypersensitivity to opioids or propofol and administration of opioids or long acting benzodiazepines within 12 h before the start of the study.

All patients were pre-medicated with diazepam 10 mg orally 1 h before surgery. Upon arrival to the anaesthetic area, midazolam 0.05 mg kg^{-1} i.v. was administered for sedation before placement of cannulae. Baseline systolic blood pressure (SBP) was recorded before instrumentation and a baseline blood sample was collected for cardiac enzyme analysis. Before induction of anaesthesia, each patient was given 100% oxygen for at least 3 min. Anaesthesia was induced with propofol 0.5 mg kg^{-1} followed by additional boluses of 10 mg every 10 s until loss of consciousness (LOC), which was defined as loss of response to verbal commands. At LOC, pancuronium 0.10–0.15 mg kg^{-1} was administered to facilitate tracheal intubation and propofol maintenance infusion 3 mg kg^{-1} h^{-1} was started. Simultaneously, as indicated by randomization, the loading dose and infusion of remifentanil placebo loading dose, 1 μg kg^{-1} min^{-1} infusion or fentanyl (15 μg kg^{-1} loading dose, placebo infusion) were started. Tracheal intubation was performed at least 6 min after the start of opioid administration.

Management of inadequate and excessive anaesthesia

During maintenance of anaesthesia, responses to surgical stimuli indicating inadequate anaesthesia were defined as one or more of the following:

- SBP >15 mm Hg above preoperative baseline or >140 mm Hg for ≥1 min; arterial pressure (AP) >80 mm Hg for ≥1 min during bypass.
- Heart rate (HR) >90 beats min^{-1} for ≥1 min (pre-bypass); non-paced HR >100 beats min^{-1} for ≥1 min (post-bypass).
- Somatic responses: gross movement, swallowing, grimacing, eye opening.
- Autonomic responses: lachrymation, sweating.

Inadequate anaesthesia was treated in a sequential manner beginning with simultaneous bolus dose administration (remifentanil 1 μg kg^{-1}, fentanyl 2 μg kg^{-1}) and infusion increments equivalent to 0.5 or 1.0 μg kg^{-1} min^{-1} remifentanil (unless there were intervening decreases). A maximum of three to six maintenance rate increases were allowed up to a maximum infusion rate of remifentanil 4 μg kg^{-1} min^{-1} or placebo equivalent. All infusion rate increases were preceded by a bolus dose. If a response was not controlled within 5 min of adjusting the opioid infusion rate or if the maximum infusion rate was reached, the propofol infusion rate was increased as required. If the response was still not controlled, other agents (e.g. sodium nitroprusside, beta-blockers) could be given. Once the patient had achieved a stable, non-responding status, the propofol infusion rate was then titrated back down but the opioid maintenance infusion was left at the higher rate unless hypotension occurred.

Excessive anaesthesia was defined as one or more of the following:

- SBP <80 mm Hg for ≥1 min; AP <40 mm Hg for ≥1 min during bypass.
- HR <40 beats min^{-1} for ≥1 min.

Hypotension was treated by administration of fluids if the patient was hypovolaemic. Otherwise these responses were treated by decreasing the opioid and/or propofol infusion rate. The opioid maintenance infusion rate was reduced by 50% of the current rate or in decrements equivalent to remifentanil 0.25–0.5 μg kg^{-1} min^{-1}. If blood pressure fell rapidly, the opioid maintenance infusion rate decrease could be accompanied by simultaneous administration of vasopressors. Further vasopressor treatment was to be used if these interventions were not successful. Bradycardia was treated by decreasing the opioid and/or hypnotic infusion rate and/or the use of anticholinergic drugs as required.

In addition to the 'treatment' of inadequate anaesthesia, the study procedure allowed preventative measures at the discretion of individual investigators. Study opioid bolus and infusion rate increases were allowed in advance of surgical stimuli to prevent anticipated responses up to a maximum infusion rate equivalent to remifentanil 4 μg kg^{-1} min^{-1}.

After surgery, once the patient was settled in the ICU, the opioid and propofol infusions were reset (remifentanil 1 μg kg^{-1} min^{-1}, placebo in the fentanyl group, propofol 0.5 mg kg^{-1} h^{-1} in both groups). The infusions were continued until the patient met the criteria for the start of weaning for extubation, that is, normothermia, haemodynamic stability (no uncontrolled arrhythmias, stable vital signs), no excessive bleeding (institutionally defined) and adequate urine output ($\geqslant$0.5 ml^{-1} kg^{-1} h^{-1}). The propofol infusion rate could be adjusted accordingly if additional sedation was required. If additional analgesia was required a bolus dose of open label morphine could be administered at the minimum dose necessary to provide patient comfort according to standard local practice and this was recorded as rescue treatment.

Once the patient had met the criteria for the start of weaning from study opioid infusion, a double-blind analgesic bolus was administered (morphine 0.15 mg kg^{-1} in the remifentanil group, placebo in the fentanyl group). The down titration period started 30 min later (as long as the patient still met the criteria for weaning from study opioid). The propofol infusion was stopped and the study opioid infusion was down-titrated at 10 min intervals in 50% decrements three to four times in order to maximize smooth transition to alternative regimens, and then discontinued. Weaning of the patient from the ventilator was started during commencement of this down-titration. If additional analgesia was required during this period, an open label bolus dose of morphine (minimum dose 0.05 mg kg^{-1}) was administered and recorded as rescue treatment.

Patients were extubated if the following criteria were met: responsive to commands; Sp_{O_2} $\geqslant$95% at FI_{O_2} $\leqslant$0.5, pH >7.25, Pa_{CO_2} $\leqslant$7.33 kPa and ventilatory frequency adequate to maintain oxygenation. If the patient had not met the criteria for beginning the extubation sequence by 4.5 h after entry into the ICU, the analgesic opioid bolus was administered at this time and the down-titration of the study opioid was then started 30 min later. Patients were eligible for transfer from ICU if stable conditions continued.

Monitoring

Vital signs were recorded immediately before induction of anaesthesia (baseline values) and at regular intervals throughout surgery and in the ICU. These consisted of SBP, DBP, MAP, HR, CVP, and Sp_{O_2}. During the pre-bypass period, patients' vital signs were recorded 1 min before and every minute for 5 min after each major surgical stress event (MSE), then every 15 min from the MSE until the next MSE. MSEs were defined as intubation, sternal skin incision, sternotomy, maximal sternal spread (MSS), and sternal wire placement. Arterial pressure was recorded at the start of cardiopulmonary bypass and every 15 min until the patient went off bypass.

After entry into the ICU, patients' vital signs were recorded immediately and at 15 min intervals thereafter until extubation. In addition, vital signs, pain, and sedation scores were recorded every 10 min during the down-titration of study opioid. Pain was assessed using a four-point patient self-rated scale (0=no pain, 1=mild, 2=moderate, 3=severe), while sedation was assessed using a five-point scale (1=fully awake and orientated, 5=eyes closed and cannot be roused by mild physical stimulation). Vital signs and pain and sedation scores were also recorded at 15, 30, 45, 60, 90, and 120 min after discontinuation of study opioid infusion.

12-lead ECG recordings were obtained within 14 days before surgery and on postoperative day 1, and at the end of day 5 or on the morning of day 6 (or day of hospital discharge if prior to this). Blood samples were obtained at 8, 16, 24, and 48 h after aortic cross clamp release for analysis of plasma cardiac enzyme concentrations (CK-CKMB).

Outcome measures

The primary efficacy endpoint was response to MSS. Secondary efficacy endpoints included responses to intubation, sternal skin incision, sternotomy, and sternal wire placement. Efficacy was evaluated by the number of patients who showed signs of inadequate anaesthesia and by the number of treatments for responses indicative of inadequate or excessive anaesthesia. Overall use of study drug, propofol and other medications were noted. Patients were continually assessed for occurrence of adverse events (including negative cardiac outcomes) throughout the perioperative period and up to the end of postoperative day 5 (or up to hospital discharge if this occurred earlier). Negative cardiac outcomes were defined as ventricular failure (requirement for postoperative intra-aortic balloon pump or ventricular assist device), myocardial infarction (CK-MB >50 unit $litre^{-1}$ and presence of new Q-waves on 12-lead ECG) or death from cardiac causes (e.g. ventricular failure or congestive heart failure) before hospital discharge.

Statistical analysis

The primary endpoint assumed a response rate of 7% and 18% for patients receiving remifentanil and fentanyl, respectively. One hundred and thirty five patients per treatment would have a power of 80% to detect this difference at a two-sided 5% level of significance. To compensate for withdrawals and to obtain additional safety data, up to 300 randomized patients were to be included in the study. The study was stopped when 297 patients had been recruited because of time restriction. Patients were randomized to receive either remifentanil or fentanyl by assignment of treatment randomization details contained in a hidden entry envelope, which had been computer-generated before the study set-up. The hidden entry envelopes were allocated sequentially to each subject eligible for study entry and the corresponding treatment allocation and drug preparation was performed by a named person, independent to the conduct of the study. In most instances this was the hospital pharmacist.

All tests of statistical significance were two-sided and carried out at the 5% level. Logistic regression analyses were used to analyse the proportions of patients with responses to MSS. Estimates of the odds ratios and 95% confidence intervals were calculated. The weighted mean pain and sedation scores during the ICU down titration were analysed using the Wilcoxon rank sum test. The treatment differences in overall use of alternate analgesics until extubation, were analysed using logistic regression analysis.

The incidences of the most commonly reported adverse events (defined as occurring in at least 5% of patients in any treatment group) were analysed using Fisher's exact test.

Results

Three hundred and twenty one patients entered the study, 24 were treated on an open label basis and were not included in the intent-to-treat population for efficacy analyses although they were included in the population for safety data. The intent-to-treat population consisted of 297 patients, of whom 148 patients received remifentanil and 149 received fentanyl.

The two groups were well matched with regard to gender, ethnic origin, age, height, weight, and ASA status distribution (Table 1). The mean ejection fraction was similar in the remifentanil (0.62) and fentanyl (0.63) groups. Most patients required three arteries to be grafted (41% in the remifentanil group and 45% in the fentanyl group). Two patients in each group had previous CABG surgery. The median durations of surgery, of bypass, and of aortic cross clamping were comparable between the two groups. The median (SD) time from the start of study drug to skin closure was 3.67 h (1.85, 6.3) in the remifentanil group and 3.58 h (1.97, 8.7) in the fentanyl group. The median (SD) durations of bypass and of aortic cross clamping were 1.31 (0.45, 2.4) and 0.75 h (0.22, 3.6), respectively, in the remifentanil group and 1.23 (0.17, 2.85) and 0.73 h (0.08, 2.33), respectively, in the fentanyl group.

Efficacy

The incidence of inadequate anaesthesia responses to MSS (the primary efficacy endpoint) was significantly lower in the remifentanil group (11%) compared with the patients in the fentanyl group (52%; $P<0.001$, odds ratio remifentanil:fentanyl= 0.09, 95% CI 0.05, 0.18). The mean remifentanil infusion rate at the time of MSS was 1.42 µg kg^{-1} min^{-1} and the mean propofol infusion rate in the remifentanil group was 3.14 mg kg^{-1} h^{-1}. In the fentanyl group, the cumulative fentanyl bolus dose administered at this point was 19.67 µg kg^{-1} and the mean propofol infusion rate was 3.94 mg kg^{-1} h^{-1}.

Hypertension was the most common type of response in those patients who had an inadequate anaesthesia response, occurring in seven patients (5%) in the remifentanil group and 75 patients (50%) in the fentanyl group. There was a mean increase in SBP (from the pre-MSS value to the maximum within 5 min of MSS) of 6 mm Hg in the remifentanil group compared with a mean increase of 15 mm Hg in the fentanyl group ($P<0.001$). A tachycardic response was recorded in 10 patients (7%) in the remifentanil group and eight patients (5%) in the fentanyl group.

Overall, the weighted mean infusion rate for remifentanil (R) during maintenance of anaesthesia (from pre-bypass to end of surgery) varied between 1.29 (0.69) µg kg^{-1} min^{-1} pre-bypass; 1.23 (0.73) µg kg^{-1} min^{-1} during bypass; 1.21 (0.77) µg kg^{-1} min^{-1} post-bypass. Fentanyl (F) cumulative bolus doses were 7.38 (3.63) µg kg^{-1} pre-bypass; 3.16 (1.56) µg kg^{-1} during bypass; and 2.92 (1.63) µg kg^{-1} post-bypass. Propofol varied between (R) 2.98 (0.69) *vs* (F) 3.58 (0.99) mg kg^{-1} h^{-1} pre-bypass; (R) 2.86 (0.45) *vs* (F) 3.46 (1.44) mg kg^{-1} h^{-1} bypass; (R) 2.8 (0.78) *vs* (F) 3.45 (1.4) mg kg^{-1} h^{-1} post-bypass; (R) 2.72 (0.85) *vs* (F) 3.32 (1.17) mg kg^{-1} h^{-1} end of surgery.

Table 1 Patient characteristics (safety population)

	Remifentanil (*n*=172)	**Fentanyl** (*n*=149)
Gender		
Male	147 (85%)	132 (89%)
Female	25 (15%)	17 (11%)
Ethnic origin		
Caucasian/white	169 (98%)	147 (99%)
Oriental	0	1 (<1%)
Asian (not oriental)	2 (1%)	0
Other	1 (<1%)	1 (<1%)
Age (yr)		
Mean (range)	62 (37–78)	63 (38–76)
SD	8 8	8.4
Height (cm)		
Mean (range)	172 (150–191)	172 (152–190)
SD	7 9	7.8
Weight (kg)		
Mean (range)	79 (50–115)	80 (54–117)
SD	11 9	11 4
ASA status		
II	38 (22%)	33 (22%)
III	124 (72%)	103 (69%)
IV	10 (6%)	13 (9%)

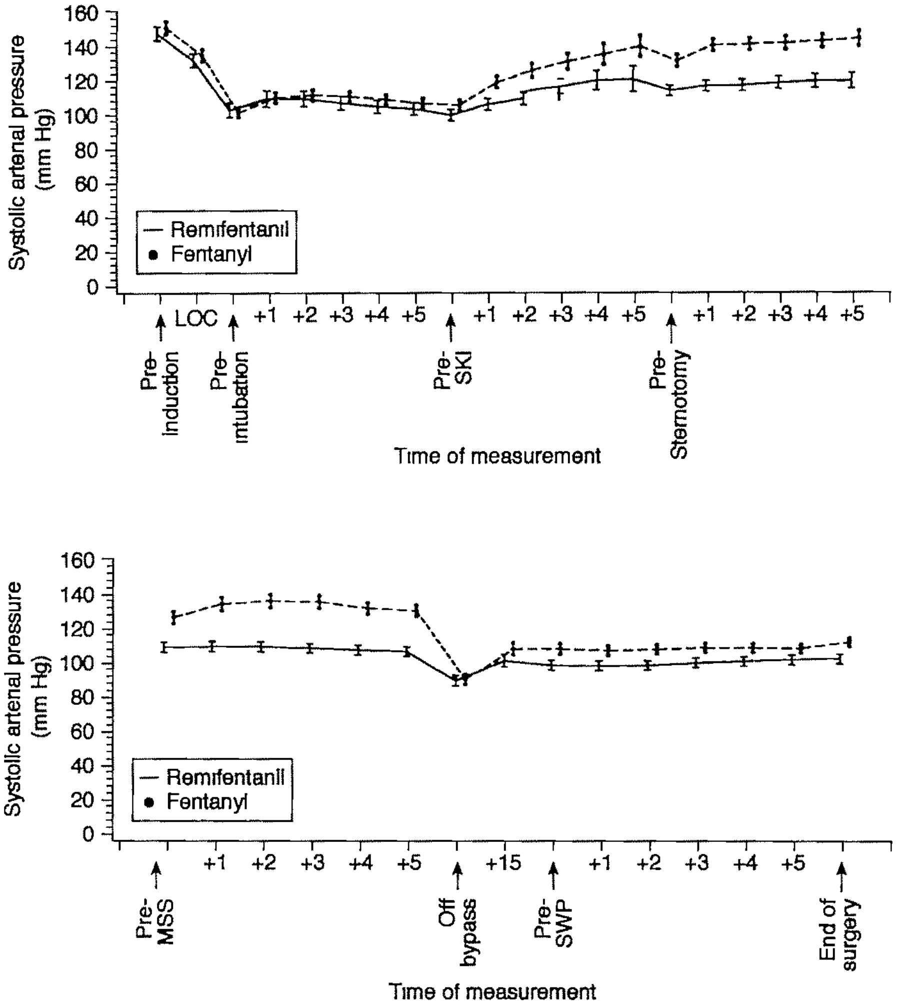

Fig 1 Mean (95% CI) intraoperative SBP in the remifentanil and fentanyl anaesthesia groups (intent-to-treat population).

During tracheal intubation, more patients in the remifentanil group showed signs of inadequate anaesthesia compared with those in the fentanyl group (R 24%, F 9%, $P<0.001$). Response to sternal skin incision (R 11%, F 36%, $P<0.001$), sternotomy (R 14%, F 60%, $P<0.001$) and MSS (R 11%, F 52%, $P<0.001$) were significantly and clinically less in the remifentanil group. During sternal wire placement no statistical or clinically significant difference was noted (R 10%, F 13%).

Figures 1 and 2 present the SBP and HR profiles during key stages during surgery for both treatment groups. SBP fell after pre-induction (baseline) but remained stable within each treatment group compared with baseline values. SBP values were higher in the fentanyl group pre- and post-skin incision compared with remifentanil values at similar time intervals. HR remained stable and similar between treatment groups compared with pre-induction values.

More patients in the fentanyl group (92%) received medication to treat inadequate anaesthesia responses compared with the patients who received remifentanil (53%). Conversely, more patients in the remifentanil group (82%) received medication to treat excessive anaesthesia responses compared with the patients who received fentanyl (60%).

Table 2 summarizes the postoperative recovery times in the remifentanil and fentanyl anaesthesia groups. The median times to eligibility for weaning for extubation, and for the actual start of the extubation sequence, were longer in the remifentanil group than in the fentanyl group ($P<0.05$). The median times to eligibility for, and the actual start of extubation were also significantly longer in the remifentanil group than in the fentanyl group ($P<0.05$). The median times to eligibility for, and for actual transfer from the ICU to less intense monitoring were similar in the remifentanil and fentanyl groups. The median times to hospital discharge were also similar in the remifentanil and fentanyl groups and a similar proportion of patients in each group (17% R, 20% F) were discharged by the end of postoperative day 5 or morning of day 6.

Pain and sedation scores were assessed at scheduled times during the ICU down titration period and following discontinuation of study drugs. The weighted mean pain score during the ICU down-titration/transition period was

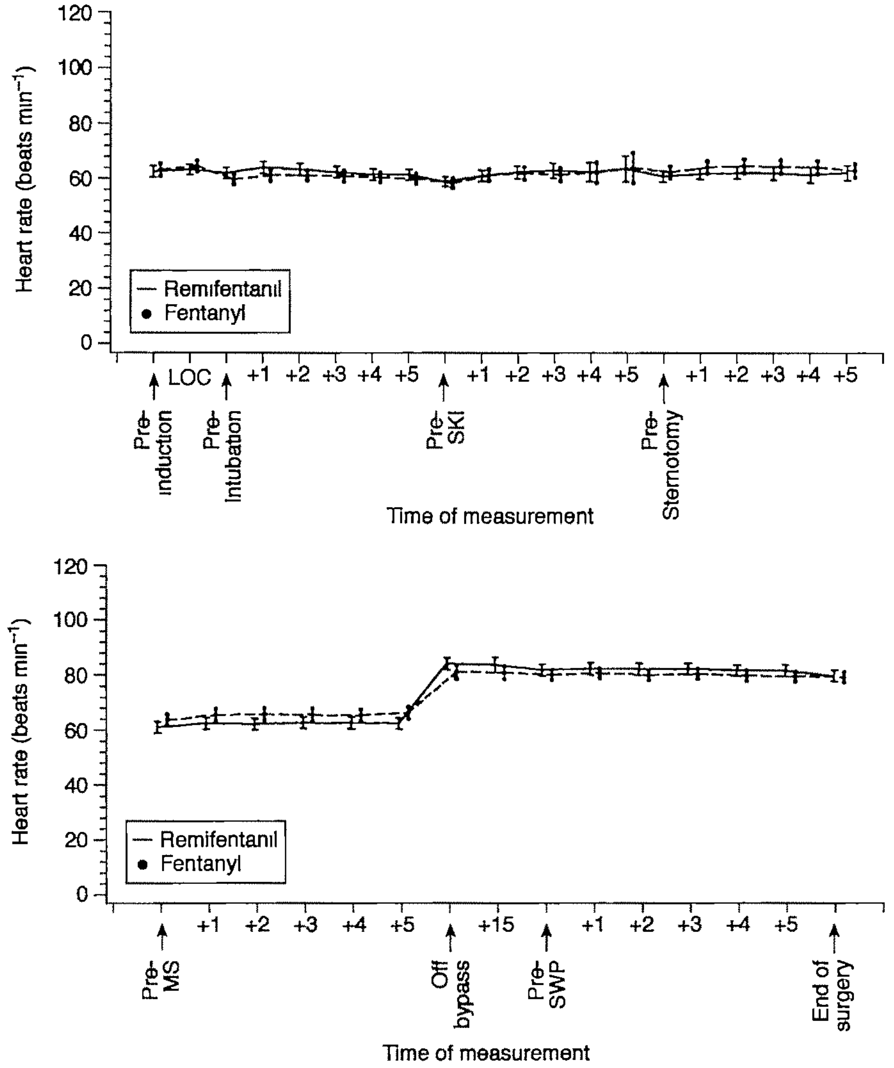

Fig 2 Mean (95% CI) intraoperative HR in the remifentanil and fentanyl anaesthesia groups (intent-to-treat population).

lower in the remifentanil group (0.21) compared with the fentanyl group (0.48). However, no significant difference in the change from baseline in pain scores between the two groups (*P*=0.174) was noted. A significantly higher proportion of patients in the remifentanil group required additional analgesia during the period from the end of surgery until extubation compared with the fentanyl group (81% *vs* 69%; *P*=0.02).

During the ICU transition period, the weighted mean sedation score was slightly but significantly higher in the remifentanil group (score 3.61) compared with the fentanyl group (score 2.92; *P*<0.001).

Safety and tolerability

Both anaesthetic regimens were well tolerated. In total, 138 patients (80%) in the remifentanil group and 113 patients (76%) in the fentanyl group experienced at least one adverse event (*P*=0.347). The most common adverse events recorded during the study (defined as events occurring in ≥5% of patients in either treatment group) are listed in Table 3. Overall, the incidences of these events were similar in the remifentanil and fentanyl anaesthesia groups, except for hypertension and shivering which had a significantly higher incidence in the remifentanil group compared with the fentanyl group (*P*<0.001 and *P*=0.049, respectively). Both of these events were most commonly reported during the ICU period. Significantly more drug-related adverse events were reported in the remifentanil group compared with the fentanyl group (R 44% *vs* F 31%, *P*=0.016). The most common drug-related adverse events were nausea (20% of patients in each group), vomiting (R 6%, F 8%) and shivering (R 11%, F 5%). The only significant differences in drug-related events between groups were hypertension during the immediate postoperative period (R 5%, F 0%, *P*=0.008) and postoperative ache(s) (R 2%, F 0%; *P*=0.016).

A total of 13 patients (remifentanil five, fentanyl eight) were withdrawn from the study because of adverse events. Of the remifentanil-treated patients who were withdrawn,

Table 2 Postoperative recovery times in the remifentanil and fentanyl anaesthesia groups (intent-to-treat population) *LIM=less intense monitoring

	Remifentanil (*n*=148)	Fentanyl (*n*=149)	*P*-value
Time (h) to eligibility for starting extubation sequence			
Median	2.4	1.8	
Range	0.0–4.6	0.0–4.8	0.038
	(*n*=143)	(*n*=149)	
Time (h) to actual start of extubation sequence			
Median	2.4	1.8	
Range	0.0–17.4	0.0–7.0	0.048
	(*n*=145)	(*n*=149)	
Time (h) to eligibility for extubation			
Median	4.9	4.1	
Range	0.2–48.6	0.4–20.2	0.016
	(*n*=145)	(*n*=148)	
Time (h) to actual extubation			
Median	5.1	4.2	
Range	0.2–48.6	0.4–20.2	0.006
	(*n*=145)	(*n*=148)	
*Time (days) to eligibility for transfer to LIM**			
Median	0.8	0.7	
Range	0.0–6.6	0.1–3.9	n.s
	(*n*=145)	(*n*=147)	
*Time (days) to actual transfer to LIM**			
Median	1.1	0.9	
Range	0.0–6.7	0.1–3.9	n.s
	(*n*=145)	(*n*=148)	
Time (days) to hospital discharge			
Median	6.9	6.1	
Range	0.0–27	0.1–58	n.s
	(*n*=139)	(*n*=140)	

two were withdrawn during the ICU anaesthesia phase, that is, from end of surgery until first down titration of the opioid infusion. In these patients anaphylactic reaction and bleeding from the chest wall, respectively, were given as the reason for patient withdrawal. Neither of these events was assessed as related to study drug. In a further three patients the phase of the adverse event was not specified. The events leading to withdrawal in these three cases were postoperative haemorrhage, left ventricular failure, and case of bleeding leading to haemodynamic instability, respectively. In the latter case, the event was considered possibly related to study drug. Of the fentanyl-treated patients who were withdrawn, one patient was withdrawn during the ICU anaesthesia phase, six during the ICU transition phase, that is, from first down-titration of opioid infusion until the infusion was discontinued and for one patient the phase was not specified. In four patients, the reason for withdrawal included bleeding or postoperative haemorrhage and two patients were withdrawn because of reasons which included myocardial ischaemia; a further two patients were withdrawn because of complete heart block and delayed recovery as a result of cerebral death. None of the events leading to withdrawal were classified as possibly related to study drug.

Table 3 Adverse events occurring in ≥5% of patients in all study phases in either treatment group (Safety Population). * Fisher's exact test

Adverse event	Remifentanil (*n*=172)	Fentanyl (*n*=149)	*P* value*
Nausea	63 (37%)	58 (39%)	n.s
Vomiting	22 (13%)	20 (13%)	n.s
Atrial fibrillation	16 (9%)	15 (10%)	n.s
Shivering	21 (12%)	8 (5%)	0.049
Fever	17 (10%)	9 (6%)	n.s
Postoperative complication	12 (7%)	9 (6%)	n.s.
Hypertension	15 (9%)	1 (<1%)	<0.001
Ache(s)	10 (6%)	5 (3%)	n.s.
Haemorrhage	10 (6%)	5 (3%)	n.s.
Hypotension	11 (6%)	4 (3%)	n.s

Serious adverse events were reported in 25 patients (15%) in the remifentanil group and in 12 patients (8%) who received fentanyl. The majority of events in both the remifentanil group (12/25, 48%) and the fentanyl group (8/12, 67%) involved the cardiovascular system. There were no reports of drug-related serious adverse events in the fentanyl group. In six patients in the remifentanil group the serious adverse events were considered to be related possibly to the study drug. These included three cases of hypertension, two of which were also associated with shivering. All three cases were considered related to the withdrawal of remifentanil during the transition to alternate analgesic regimens. There were three serious cases of respiratory depression in the ICU in the remifentanil group, all of which resolved. In one of these cases the patient had a history of sleep apnoea.

A similar proportion of patients in each group showed signs of ischaemia during the perioperative period (13% of patients in the remifentanil group and 10% of those in the fentanyl group; P =0.44). Only one of these episodes in the fentanyl group was reported as a drug-related adverse event. There was also no significant difference between the two treatment groups in the incidence of negative cardiac outcomes (ventricular failure, myocardial infarction or death as a result of cardiac causes). Ventricular failure was reported in two of 146 patients (1%) in the remifentanil group; myocardial infarction was reported in four of 146 patients (3%) and three of 148 patients (2%) in the remifentanil and fentanyl groups, respectively (P=0.689). There were no deaths as a result of cardiac causes before hospital discharge. None of the three deaths reported during the study were considered to be related to the study drug.

Discussion

Our data demonstrate that the combination of remifentanil (starting dose of 1 $\mu g\ kg^{-1}\ min^{-1}$) and propofol (starting dose 3 $mg\ kg^{-1}\ h^{-1}$) was significantly more effective than the low/medium-dose fentanyl regimen used in obtunding responses to the majority of MSEs studied, including the primary endpoint, MSS. An exception to this was the higher incidence of responses to tracheal intubation in the remifentanil group compared with fentanyl-treated patients. One could argue that the high bolus dose of fentanyl at the start of anaesthesia enabled optimal obtunding of the stress response since the peak effects of fentanyl occur between 3 and 6 min after administration.[9] However, stable intubation conditions with remifentanil could be expected after 6 min of a continuous infusion.[10] It is, therefore, difficult to explain why higher response rates to intubation were observed with remifentanil.

Intraoperative infusion rates indicate that 1 $\mu g\ kg^{-1}\ min^{-1}$ was an appropriate starting dose for remifentanil, which could be subsequently titrated up or down to the effect required in the individual patient. The minimum and maximum dose of remifentanil administered, reflect the wide inter-patient variability in the dose required to achieve adequate analgesia with an opioid in combination with the hypnotic component. Similar variations in initial remifentanil dose requirements for cardiac surgery are reported in the recent literature. [11–15]

Hypertension was the most commonly treated inadequate anaesthesia response in both groups, although the incidence was much higher in the fentanyl group. The majority of patients in both treatment groups (78% remifentanil *vs* 77% fentanyl) were receiving beta-blockers before the start of study treatment, which may help explain the very low incidence of tachycardia observed as a response to the major stress events.

It is recognized that opioids interact with such agents and blunt the sympathetic response to stress events and may exacerbate bradycardic and hypotensive episodes. Indeed recent reports of clinically significant bradycardia with use of remifentanil in cardiac patients [16 17] have cautioned its use in such patient groups although our experience did not indicate clinically significant treatment differences in bradycardia. Where hypotension did occur, the episodes were transient and managed by appropriate measures which included fluid loading, infusion rate adjustments of remifentanil and propofol and pharmacological intervention as required.

After transport to the ICU, both groups received the same starting infusion of propofol in combination with an opioid infusion (placebo in the fentanyl group). The mean pain score during the ICU transition period (i.e. down titration to alternate postoperative pain management regimens) was comparable between treatment groups. The pharmacokinetic profile of remifentanil may be expected to result in a rapid offset of action. Indeed there were some reports of hypertension and shivering observed during the transition from a remifentanil regimen to an alternative postoperative regimen, which may have been as a result of suboptimal management of the rapid offset of effects of remifentanil with respect to transition to alternative analgesics. The transition to an effective alternative analgesic regimen is a key consideration in the postoperative management of the patient when using a remifentanil regimen. Morphine administration as adopted in this study, may not be the best solution for fast track anaesthesia, although its cautious use during remifentanil based cardiac anaesthesia may have its place. Alternative and effective transition regimens have been suggested in the literature. [14 18]

Patients who received the low/medium-dose fentanyl regimen were eligible for extubation and were extubated earlier than the patients who received remifentanil. This may relate to the higher level of sedation in the remifentanil-treated patients during the postoperative period, which may have influenced the investigators' decision as to whether to actively intervene in extubating an otherwise calm and sedated patient. Similar consideration in actively managing early extubation regimens has been reported in the literature.[19] It would, therefore, appear that proactive intervention may be necessary with regard to extubation when using this dose of remifentanil in combination with propofol for weaning. In contrast, alternate transition regimens to that administered in this study have demonstrated comparable or superior recovery compared with a fast track fentanyl regimen.[13 15]

Despite the longer time to extubation in the remifentanil group compared with fentanyl-treated patients, there were no statistically significant differences between the two groups in the median times to eligibility for, or actual transfer from the ICU to less intense monitoring or to hospital discharge. The data probably reflect the fact that although the protocol-specified anaesthetic and postoperative treatment regimens ensured that patients could be extubated within a reasonable timeframe, subsequent management of patients would largely have depended upon whether or not hospital procedures were in place to 'fast track' patients to hospital discharge. It was not possible to standardize these in this large multi-centre international study. This is supported by the fact that in the majority of cases where patients were not discharged from hospital by the end of postoperative day 5, the reasons listed included institutional practice rather than any influence of the anaesthetic regimen used. Similar observations have been reported in other studies in which early extubation and recovery has not always resulted in faster ICU and/or hospital discharge times.[4 7 20] In this regard, it is also notable that many of the studies that have demonstrated significant reductions in ICU and/or hospital stay were conducted at single centres, [4 7 21 22] reducing the impact of variations in procedures for extubation, ICU, and hospital discharge. However, in this study, the use of the 'high dose' remifentanil opioid regimen resulted in a similar duration of ICU stay and postoperative hospitalization as the fentanyl regimen.

Both anaesthetic regimens were well tolerated and the recorded adverse event profiles are typical of potent μ-opioid receptor agonists and predictable in these patients following CABG surgery. There was little difference in the overall incidence of adverse events between the remifentanil and fentanyl treatment groups, although the incidences of drug-related adverse events and of serious adverse events were higher in the remifentanil group than in the fentanyl group. Postoperative shivering and hypertension can increase oxygen consumption and precipitate episodes of myocardial ischaemia, which may adversely influence outcome, including risk of myocardial infarction.[2,23] However, the increased frequency of hypertensive events in the remifentanil group compared with the fentanyl group was not associated with any significant difference in the incidence of perioperative negative cardiac outcomes.

The serious cases of postoperative respiratory depression observed in the remifentanil group is an unexpected finding given the rapid offset of action of remifentanil. However, of the three reported cases, one included a patient with an underlying sleep apnoea disorder. Administration of the active blinded morphine bolus doses in the remifentanil group may have contributed to the higher incidence of respiratory depression observed compared with the placebo-treated fentanyl group.

In summary, our data show that high-dose remifentanil in combination with propofol is effective and well-tolerated when used to provide anaesthesia in CABG patients. Importantly, the data show that the remifentanil regimen provided superior control of some of the major stress events, but not to intubation. Intraoperative haemodynamic stability was associated with both treatment groups but use of a high-dose remifentanil regimen did not compromise patients' overall recovery times compared with the low/medium-dose 'fast track' fentanyl regimen. However, transition from a remifentanil-based regimen to alternate postoperative pain management regimens must be carefully and proactively managed to ensure rapid and smooth transition to alternate analgesic regimens.

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Effect of epidural bupivacaine *vs* combined epidural bupivacaine and morphine on gastrointestinal function and pain after major gynaecological surgery

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In a double-blind study, we investigated the effects of postoperative epidural local anaesthetic, with or without addition of epidural morphine, on postoperative pain and gastrointestinal function in patients scheduled for radical hysterectomy and pelvic lymphadenectomy. Forty patients were randomized into two study groups: 48-h postoperative epidural 0.2% bupivacaine 8 ml h^{-1} (bupi group) or 48-h postoperative epidural 0.2% bupivacaine/morphine 50 µg at 4 ml h^{-1} (bupi/morph group). Patients were observed for at least 96 h after surgery. No differences in pain at rest, during cough or mobilization were observed. Patients in the bupi group requested a significant greater amount of supplementary analgesics, but times to first flatus and defaecation were reduced compared with patients in the bupi/morph group. Itching was a significant problem in patients in the bupi/morph group. No differences in postoperative nausea and vomiting, mobilization or time to discharge from hospital were observed between groups. The addition of morphine to postoperative epidural bupivacaine has only limited effect on pain relief and increases time to normalization of gastrointestinal function.

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Major gynaecological surgery is associated with severe postoperative pain, prolonged gastrointestinal paralysis and a high incidence of postoperative nausea and vomiting (PONV).[1–6] Postoperative gastrointestinal paralysis is well known after surgery and severe trauma. Although worsened if the peritoneum is entered, the duration of surgery does not influence the severity of postoperative gastrointestinal ileus.[7] The pathophysiology of postoperative alterations in gastrointestinal motor function is complex and has not been clarified. Experimental studies show activity in spinal efferents, inhibitory non-adrenergic non-cholinergic vagal efferent nerves and in sympathetic efferent nerves, but the peptidergic neuronal systems of the enteric nervous system have still not been elucidated.[6–8]

Administration of epidural local anaesthetics results in effective pain relief and improved gastrointestinal motility compared with opioid-based analgesia after hysterectomy.[5 6] In healthy volunteers, epidural bupivacaine alone does not affect gastric emptying or bowel function,[9 10] whereas addition of epidural opioid delays gastric emptying and prolongs orocaecal transit time.[11]

Only two randomized studies comparing postoperative epidural local anaesthetic with combined local anaesthetic and opioid have evaluated both gastrointestinal recovery and postoperative pain after laparotomy.[12 13] In the study by Asantila and colleagues,[12] analgesia with the combination of bupivacaine and morphine was superior to that with bupivacaine alone. However, gastrointestinal recovery was delayed in patients receiving the combination. In the study by Liu and colleagues,[13] no significant differences in either analgesia or time to first postoperative flatus was observed between patients receiving bupivacaine and those receiving bupivacaine combined with morphine.

The aim of this study was to investigate the effect of continuous thoracic epidural bupivacaine alone *vs* combined epidural bupivacaine and morphine on postoperative gastrointestinal function and pain after radical hysterectomy and pelvic lymphadenectomy.

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Patients and methods

We studied 40 patients aged 18–75 yr undergoing radical hysterectomy and pelvic lymphadenectomy through an inferior median incision. Informed written consent was obtained from all patients and approval was obtained from the local ethics committee and the Danish National Board of Health. Patients were recruited from the Department of Gynaecology, Herlev University Hospital between February 1999 and October 2000. Patients were not included if they were unable to cooperate, body weight was $\geqslant$[1.3×body height (cm)–100], had a history of drug or alcohol abuse, chronic pain or daily intake of analgesics or had contraindications to non-steroidal anti-inflammatory drugs (NSAIDs) or to insertion of an epidural catheter.

The study was double-blind and randomized with a computer program. The study drugs (bupivacaine 2 mg ml^{-1} and bupivacaine 2 mg ml^{-1}/morphine 50 μg ml^{-1}) were prepared by the hospital pharmacy in identical containers marked with the name of the project, the investigator's name and consecutive numbers. One hour before surgery, patients received sublingual triazolam 0.125 mg. Before induction of general anaesthesia, an 18-gauge epidural catheter was inserted through a Touhy needle and advanced 4–5 cm into the epidural space at the T10–11 level and a 4-ml test dose of lidocaine 20 mg ml^{-1} with epinephrine was administered. A bolus dose of 16 ml of lidocaine 20 mg ml^{-1} with epinephrine was administered, followed by continuous infusion of lidocaine 20 mg ml^{-1} at 8 ml h^{-1} throughout the operation.

General anaesthesia was induced with propofol 1.5–2.5 mg kg^{-1}, alfentanil 1.0 mg and rocuronium 0.6 mg kg^{-1}, and an endotracheal tube was passed. Propofol without nitrous oxide was given for maintenance of anaesthesia. Further alfentanil 1.0 mg was administered at the discretion of the anaesthetist. Hypotension was treated by i.v. infusion of isotonic sodium chloride, HAES 6% or ephedrine 5 mg i.v. in incremental doses when systolic blood pressure was below 90 mm Hg. Fluid and blood losses were replaced according to the prescriptions of the department.

At skin closure, patients were randomized to receive an epidural bolus dose of 8 ml bupivacaine 2 mg ml^{-1} followed by a continuous epidural infusion of bupivacaine 2 mg ml^{-1} at 8 ml h^{-1} for 48 h (bupi group) or 4 ml bupivacaine 2 mg ml^{-1}/morphine 50 μg ml^{-1} followed by a continuous epidural infusion of bupivacaine 2 mg ml^{-1}/morphine 50 μg ml^{-1} at 4 ml h^{-1} for 48 h (bupi/morph group). Administration of the epidural bolus dose and initiation of the Deltec pump (Pharmacia) for the postoperative epidural infusion were performed by a person not involved in postoperative data collection or pain assessment. During the 48 h of infusion, the Deltec pump was covered by a box, so blinding the patient and assessors. For the first 48 h after surgery, all patients received paracetamol 2 g rectally every 8 h. For the first 72 h after surgery, ketorolac 15 mg was administered i.m. with a minimum interval of 8 h, on patient demand. If additional analgesic was required before another dose of ketorolac could be administered, morphine 0.125 mg kg^{-1} was given i.m. In the recovery ward, morphine 0.0625 mg kg^{-1} i.v. was administered on patient demand.

Patients were given ondansetron 4 mg i.v. with a lockout period of 8 h if they required an antiemetic. If additional antiemetic was required before another dose of ondansetron could be administered, metoclopramide 10 mg i.v. was given.

Before surgery, all patients were instructed in the use of the visual analogue scale (VAS) pain score, and to request supplementary analgesics and antiemetics if needed. VAS pain scores (0 mm = no pain, 100 = worst pain imaginable) at rest, on coughing and at mobilization from the supine to the sitting position were assessed by the patients 4, 6, 24, 48, 50, 54, 72 and 96 h after surgery. The numbers of ketorolac and morphine doses were recorded at the same intervals. Levels of sensory block to pinprick bilaterally were assessed 6, 24, 48, 50 and 54 h after surgery. In the event of asymmetrical blockade, the greater spread was recorded. Motor block was assessed using a four-point modified Bromage scale (0 = no motor block, 1 = inability to raise extended legs, 2 = inability to flex knees, 3 = inability to flex ankle joints) 6, 24, 48, 50 and 54 h after operation. Ability to walk (0 = no difficulty, 1 = little difficulty, 2 = very difficult, 3 = impossible, 4 = difficult or impossible for other reasons than motor block) was assessed 6, 24, 48, 50 and 54 h after surgery. The actual duration of mobilization (<1, 1–4 or >4 h) during the 24–48 and 48–72 h intervals was assessed 48 and 72 h after surgery. Patients who were not able to mobilize after >4 h were asked the primary reason for this.

At all visits, gastrointestinal function was assessed by asking the patients if and when they noted first flatus and stool, and if they had experienced nausea (0 = no, 1 = light, 2 = moderate, 3 = severe) and/or vomiting since the last assessment. Patients were encouraged to eat and drink whenever possible after the operation. Ingestion of predefined quantities of food and beverages was assessed at 24, 48 and 72 h.

Every 24 h after surgery, patients were assessed as ready or not ready for discharge from hospital by four discharge criteria: (1) normal defaecation and no urinary retention; (2) able to mobilize and dress; (3) need for opioid; (4) surgical complication requiring hospitalization. When the patient replied 'yes' to the first two and 'no' to the last two questions, he or she was declared ready for discharge from hospital.

The primary end-point of this study was time to first postoperative defaecation. Calculation of sample size was based on an unpublished pilot study performed at our institution and a previous study of postoperative gastrointestinal function after hysterectomy.[12] For calculation, the following variables were used: type 1 error 5%; type 2 error 20%; minimal difference not to be overlooked, 24 h reduction in time to first postoperative stool in the bupi

Table 1 Patient and perioperative characteristics [median (range) or number]. No significant differences

	Group	
	Bupi	**Bupi/morph**
No of patients at t=0	19	20
No. of patients at t=24	17	19
No. of patients at t=48	17	19
Age (yr)	41 (26–69)	43 (27–71)
Weight (kg)	66 (42–74)	62 (47–95)
Height (cm)	169 (150–175)	168 (157–176)
Duration of surgery (min)	185 (130–280)	180 (127–280)
Peroperative propofol (mg)	2440 (1427–3266)	2123 (1070–3300)
Peroperative alfentanil (mg)	1 (1–3)	1 (1–3)
Peroperative haemorrhage (ml)	600 (200–1200)	500 (200–1900)
Peroperative SAG M (ml)	0 (0–600)	0 (0–600)
Peroperative sodium chloride (ml)	2000 (1000–3000)	2000 (1200–3600)
Peroperative 6% HAES (ml)	500 (0–2000)	1000 (0–2000)
Peroperative ephedrine (mg)	0 (0–55)	0 (0–45)

Table 2 VAS pain scores (0–100 mm) at rest [median (interquartiles)]

Postoperative time	**Group**		***P***
	Bupi	**Bupi/morph**	
4 h	2 (1–15)	11 (3–19)	0.19
6 h	3 (0–8)	3 (0–10)	0.92
24 h	2 (0–13)	0 (0–7)	0 31
48 h	4 (0–7)	0 (0–3)	0 03
50 h	10 (2–31)	2 (0–12)	0.08
54 h	5 (1–18)	4 (0–11)	0.24
72 h	3 (0–8)	7 (0–13)	0 26
96 h	4 (2–16)	5 (0–20)	0 79

Table 3 VAS pain scores during cough [median (interquartiles)]

Postoperative time	**Group**		***P***
	Bupi	**Bupi/morph**	
4 h	7 (4–40)	20 (12–44)	0 17
6 h	16 (8–28)	17 (6–30)	0 94
24 h	16 (4–43)	16 (5–43)	0 95
48 h	20 (4–38)	11 (5–22)	0 36
50 h	26 (9–54)	18 (8–28)	0 50
54 h	20 (6–45)	14 (7–32)	0 63
72 h	13 (3–35)	25 (13–35)	0 27
96 h	22 (4–35)	22 (7–26)	0.72

Table 4 VAS pain scores during mobilization [median (interquartiles)]

Postoperative time	**Group**		***P***
	Bupi	**Bupi/morph**	
4 h	16 (3–48)	25 (12–39)	0.31
6 h	17 (7–46)	18 (6–29)	0.84
24 h	12 (4–40)	14 (2–29)	0 97
48 h	7 (2–19)	12 (4–18)	0.48
50 h	16 (6–38)	14 (10–28)	0 96
54 h	20 (6–32)	19 (6–28)	0 79
72 h	11 (3–31)	20 (9–35)	0 37
96 h	9 (4–18)	10 (8–26)	0 23

group; standard deviation of mean time to first postoperative defaecation, 24 h. The sample size needed to demonstrate this difference was 15 in each group. Statistical analyses were performed using the Mann–Whitney rank sum test for unpaired data, the Wilcoxon signed rank sum test for paired data and Fisher's exact test for dichotomous data, where appropriate. A Cox regression analysis with time to first postoperative flatus and defaecation as dependent variable was performed. Independent covariates chosen beforehand were treatment group, duration of operation, dose of supplementary morphine administered before the event, and age of the patient. If multiple testing was performed, significant P values were corrected with a Bonferroni factor for multiple comparisons. $P<0.05$ was considered statistically significant. Calculations were performed using SPSS 9.5 for Windows.

Results

We considered 53 consecutive patients for inclusion in the study. Thirteen were not included: five used analgesics or had a history of alcohol abuse; three had contraindications to NSAIDs; one had preoperative chemotherapy; one did not want to participate; in one it was not possible to insert an epidural catheter; in one the preoperative epidural bolus dose produced a heterogeneous sensory block; and in one the epidural catheter became occluded during the operation. Thus, 40 patients were included in the study. Four of these were excluded during the study period, one because of change in surgical approach and three at 24 h (severe hypotension, accidental removal of the epidural catheter and withdrawal of consent because of severe itching). The patient with severe itching was in the bupi/morph group and the other three patients were in the bupi group.

There were no significant differences between groups with respect to patient or operative characteristics (Table 1). In particular, intraoperative hypotension was not a problem and only nine and six patients in the bupi and the bupi/morph groups respectively needed i.v. ephedrine.

There were no significant differences between groups for VAS pain scores at rest, during cough or during mobilization from the supine to the sitting position at any time (Tables 2–4).

VAS pain scores increased significantly in both groups at rest, during cough and during mobilization from 48 to 50 h after surgery, after the epidural catheters had been removed ($P<0.03$). Patients in the bupi group requested significantly greater amounts of supplementary ketorolac and morphine from 24–48 h compared with the bupi/morph group (Tables 5 and 6).

According to the Cox regression analysis, times to first postoperative passage of flatus and defaecation were significantly shorter in the bupi group than in the bupi/morph group (flatus, P=0.03; defaecation, P=0.02) (Fig. 1A and B). Times to first postoperative flatus and defaecation

Table 5 Number of patients who requested ketorolac and number of doses administered. *$P<0.05$ after Bonferroni correction

Postoperative period	Group		*P*
	Bupi	Bupi/ morph	
0–24 h			
No. of patients receiving ketorolac	19/19	19/20	1.0
No. of doses in patients receiving ketorolac	38	25	0.021*
24–48 h			
No. of patients receiving ketorolac	15/17	4/18	0.001*
No. of doses in patients receiving ketorolac	22	8	0.006*
48–72 h			
No. of patients receiving ketorolac	14/17	15/18	1.0
No. of doses in patients receiving ketorolac	27	32	0.53

Table 6 Number of patients who requested morphine and number of doses administered. *$P<0.05$ after Bonferroni correction

Postoperative period	Group		*P*
	Bupi	Bupi/ morph	
0–24 h			
No. of patients receiving morphine	18/19	18/20	0.13
No. of doses in patients receiving morphine	43	28.5	0.07
24–48 h			
No. of patients receiving morphine	9/17	2/19	0.03*
No. of doses in patients receiving morphine	12	2	0.02*
48–72 h			
No. of patients receiving morphine	11/17	7/19	0.18
No. of doses in patients receiving morphine	24	11	0.15

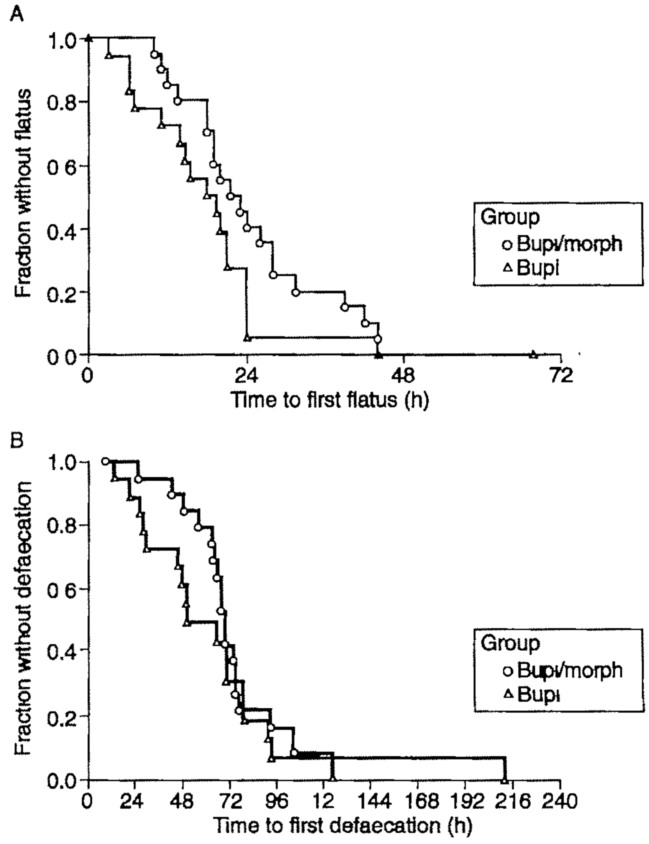

Fig 1 Survival plots of times to first flatus (A) and first defaecation (B). Time was reduced significantly in the bupi group (flatus, $P=0.03$, defaecation, $P=0.02$; Cox regression analysis).

were significantly influenced by dose of supplementary morphine administered before the event. Duration of surgery and age of the patient did not have any influence on times to first postoperative flatus or defaecation, according to the Cox regression analysis. One patient in the bupi group suffered severe postoperative paralytic ileus. On day 5, she had a rectal tube inserted with some benefit. Her first postoperative spontaneous defaecation was 212 h after surgery. This patient was included in all analyses.

There were no differences in the spread of sensory block or motor block at any assessment. Only three of 17 (18%) patients in the bupi group compared with six of 19 (32%) in the bupi/morph group and seven of 17 (41%) in the bupi group compared with eight of 19 (44%) in the bupi/morph group were able to walk without difficulty at 24 and 48 h (no significant difference). In 10 of 17 (59%) patients in the bupi group compared with 13 of 19 (68%) in the bupi/morph group and in six of 17 (35%) in the bupi group compared with 10 of 19 (53%) in the bupi/morph group, ability to walk could not be evaluated for reasons other than motor block (no significant difference). In both groups, the primary reason for this was dizziness in approximately 70% of the patients 24 and 48 h after surgery.

There was no difference between groups in mobilization time 24–48, 48–72 or 72–96 h after surgery. At 24–48 h, 11 and 16% of patients in the bupi group and bupi/morph groups respectively mobilized for more than 4 h. At 48–72 h the corresponding numbers were 29 and 21% and those at 72–96 h were 59 and 58%.

The two groups had similar incidences of nausea and vomiting (Table 7). There were no significant differences in the number of patients requesting antiemetics or the number of doses (Table 8). Nausea was mild in most patients; however, nine patients (five in the bupi group and four in the bupi/morph group) experienced severe nausea. Nine patients reported nausea of very short duration (minutes) during attempts to mobilize. The incidence of itching was significantly different in the two groups. At 24 h, one patient in the bupi group compared with nine in the bupi/morph group suffered itching ($P=0.008$) and at 48 h the corresponding numbers were one and eight ($P=0.02$) (Table 7). Furthermore, 24 h after surgery one patient in the bupi/morph group withdrew consent because of intolerable itching.

All patients had an indwelling bladder catheter for 4 days. Therefore, no patients experienced urinary retention.

There were no significant differences between groups with respect to amount and time to ingestion of food and beverages. Patients fulfilled discharge criteria a median of 5

Table 7 Number of patients who experienced nausea and/or vomiting since last assessment, and number of patients suffering from itching. *$P<0.05$ after Bonferroni correction

Postoperative period	Group		*P*
	Bupi	Bupi/ morph	
0–24 h			
No. of patients experienced nausea	5/19	9/20	0.32
No of patients who vomited	6/19	7/20	1.0
No. of patients suffering from itching	1/19	9/20	0.016*
24–48 h			
No of patients experienced nausea	6/17	9/19	0.52
No. of patients who vomited	3/17	7/19	0.27
No. of patients suffering from itching	1/17	8/19	0.04*
48–72 h			
No. of patients experienced nausea	5/17	4/19	0.71
No. of patients who vomited	3/17	1/19	0.33
No of patients suffering from itching	0/17	0/19	1.0

Table 8 Number of patients who requested antiemetics (ondansetron or metoclopramide) and number of doses administered

Postoperative period	Group		*P*
	Bupi	Bupi/ morph	
0–24 h			
No. of patients receiving antiemetics	8/19	11/20	0.52
No. of doses in patients receiving antiemetics	9	16	0.26
24–48 h			
No of patients receiving antiemetics	6/17	8/19	0.74
No of doses in patients receiving antiemetics	8	20	0.45
48–72 h			
No. of patients receiving antiemetics	4/17	5/19	1.0
No. of doses in patients receiving antiemetics	4	13	0.68

(quartiles 4–7) days and 6 (5–7) days after operation in the bupi and bupi/morph groups respectively (not significant).

Discussion

Provided that the epidural catheter is placed at the correct intervertebral space, epidural analgesia with local anaesthetic is a powerful method of relieving postoperative pain.[14] After abdominal surgery, the combination of epidural local anaesthesia and opioid has been shown to produce superior pain relief compared with the same dose of epidural local anaesthesia alone.[1 12 15–18] Very few studies have focused on both postoperative pain relief and postoperative gastrointestinal paralysis. Improved pain relief may be at the expense of impaired gastrointestinal function.[5]

This study was designed to compare the effects of postoperative epidural bupivacaine 2 mg ml^{-1}/morphine 50 $\mu g\ ml^{-1}$ with the effects of the double dose and volume of epidural bupivacaine alone, on pain and gastrointestinal function. Because of the lack of dose–response data for epidural bupivacaine, the dose administered to patients receiving epidural bupivacaine alone was chosen on the basis of a previous study conducted at our institution.[19] Intra- and postoperative administration of opioids was restricted and standardized to reduce gastrointestinal paralysis and PONV. Thus, paracetamol was administered to all patients and ketorolac was the first-choice escape analgesic. Morphine was administered after surgery only if ketorolac was insufficient.

We showed no differences in VAS pain scores at rest, or during cough and ambulation between the study groups at any time, but a significantly increased need for both ketorolac and morphine in patients receiving bupivacaine alone. This is a clear indication that the combination of epidural local anaesthetic and opioid provides superior analgesia compared with the double dose of epidural local anaesthetic alone.

Regression analysis showed a reduction in time to restoration of gastrointestinal function in the bupi group compared with the bupi/morph group; there was a mean difference of 3 h to first postoperative flatus and 18 h to first postoperative defaecation. These results are in accordance with the findings by Asantila and colleagues[12] and demonstrate that either omitting a small dose of epidural morphine or an increased dose of bupivacaine may improve the restoration of gastrointestinal function. Furthermore, regression analysis indicated that prolongation of time to first defaecation was associated with administration of supplementary systemic morphine.

As in previous studies,[20] administration of epidural morphine was associated with itching in almost 50% of patients and one patient withdrew from the study because of this side-effect. A high incidence of this relatively minor side-effect may be acceptable if the patients get clear benefits. In this study, however, the benefit of the epidural combination of local anaesthetic and opioid was restricted to a reduced need for supplementary analgesics. Gastrointestinal function was impaired, itching was a significant problem and no other differences in side-effects were demonstrated. However, we studied a small number of patients, so conclusions should be guarded.

In summary, in patients undergoing major gynaecological surgery with free access to postoperative ketorolac and systemic morphine, epidural bupivacaine alone resulted in reduced gastrointestinal paralysis and itching, but similar pain relief and PONV, when compared with epidural bupivacaine and morphine. Under the conditions of this study, no effect on recovery or time to discharge from hospital was observed.

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Intrathecal ropivacaine or bupivacaine with fentanyl for labour

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Combined spinal-epidural (CSE) is widely used to provide pain relief in labour while minimizing motor blockade. Aiming to further reduce associated motor weakness, we compared ropivacaine 2.5 mg in the intrathecal injection with a standard bupivacaine CSE in a double-blind study. Forty women were randomized to receive either bupivacaine 2.5 mg or ropivacaine 2.5 mg intrathecally, both with fentanyl 0.025 mg. There were no significant differences between the groups regarding the onset, duration or quality of analgesia or the level of sensory block attained. Forty per cent of the women (8/20) receiving bupivacaine developed detectable motor block compared with only 5% (1/20) in the ropivacaine group ($P<0.05$). Vibration sense was impaired in one woman in each group. Adverse effects did not differ between groups. We conclude that intrathecal ropivacaine 2.5 mg in combination with fentanyl 0.025 mg as part of a CSE technique provides rapid and safe analgesia for labour as effective as that achieved with bupivacaine 2.5 mg and with significantly less motor block.

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Current obstetric analgesic practice aims to provide effective pain relief while minimizing motor blockade. Lowering the concentration of bupivacaine in epidural infusions has reduced the occurrence of motor blockade but even with dilute bupivacaine infusions moderate to severe motor blockade has been shown to occur in almost 44% of women.[1] Motor blockade has been shown to reduce maternal satisfaction with epidural analgesia.[2]

Efforts to improve epidural analgesia led to Collis and colleagues[3] popularizing the combined spinal-epidural technique (CSE) for analgesia in labour. This technique involved an initial intrathecal injection of opioid (fentanyl) and bupivacaine to establish analgesia, and subsequent epidural injections to restore and maintain analgesia. The doses of drugs involved were such that ambulation in labour was possible.

However, after the initial intrathecal injection, motor blockade may be present for up to 20 min. Recent research has shown that, in the absence of motor weakness, there is no functional impairment of balance after CSE analgesia in labouring women[4] and therefore ambulation is safe.

Ropivacaine is a newer local anaesthetic which has been shown to cause less motor weakness by the epidural route while still providing effective analgesia. Ropivacaine has been used for spinal analgesia in general surgical patients, in whom doses of 15 and 22.5 mg were shown to be effective without major side-effects.[5 6] More recently, intrathecal ropivacaine has also been used to provide analgesia in labour as part of a CSE technique.[7] In that study the opioid used was sufentanil.

The aim of this study was to compare the routine intrathecal injection used in our unit, fentanyl 0.025 mg and bupivacaine 2.5 mg, with an intrathecal injection of fentanyl 0.025 mg and ropivacaine 2.5 mg. Efficacy, sensory and motor blockade and fetal effects were studied in detail.

Methods

After Research Ethical Committee permission and written informed consent had been obtained, 40 women in labour requesting regional analgesia were invited to participate in this study. Women who had received any parenteral opioid in the preceding 24 h were excluded from the study. A standardized technique was used, as detailed below. An i.v. infusion of 1 litre Hartman's solution was started and, with the women in the sitting position, a no. 18 Tuohy needle was inserted at the L2–3 or L3–4 interspace. The epidural space was identified by loss of resistance to saline and a needle-through-needle technique was used to perform an intrathecal injection over 10 s. An epidural catheter was then

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Table 1 Patient characteristics. Mean (SD or range) values are as appropriate

	Ropivacaine/ fentanyl (*n*=20)	**Bupivacaine/ fentanyl (*n*=20)**
Age (yr)	27 (18–36)	28 (18–39)
Height (cm)	162 (5 2)	161 (6.3)
Weight (kg)	78 (12 8)	81 (13 2)
Gestation (weeks)	40 0 (37–41)	40 5 (38–41)
Dilatation of cervix (cm)	3.8 (1 3)	3 2 (1.1)
Primigravida (*n*)	7/20	10/20

Table 2 Analgesia and block characteristics in patients given the drugs shown by intrathecal injection Mean (SD) or median (range)

	Ropivacaine/ fentanyl (*n*=20)	**Bupivacaine/ fentanyl (*n*=20)**
Onset of analgesia (min)	6.5 (2.3)	6 5 (2.3)
Duration of analgesia (min)	64 (21)	74 (19)
Max sensory level (pinprick)	T6 (T9–T2)	T5 (T8–T2)
Max sensory level (ice)	T5 (T8–T1)	T3 (T8–T1)

passed, leaving 3 cm in the epidural space. A single operator was involved in all cases (DH) and the position of the catheter was checked by aspiration for blood or CSF.

The women were given an intrathecal injection of one of two anaesthetics by random allocation. Those in group B received bupivacaine 2.5 mg with fentanyl 0.025 mg made up to a total volume of 2 ml. Those in group R received ropivacaine 2.5 mg with fentanyl 0.025 mg, also made up to 2 ml with normal saline. Both the patient and the observer were blinded to the contents of the intrathecal injection, the same two observers being involved in all cases. The study period commenced after the intrathecal injection and finished at request for further analgesia by epidural bolus.

Maternal heart rate and arterial blood pressure (non-invasive) were recorded at 2-min intervals for the first 20 min and at 5-min intervals thereafter. Hypotension, defined as a drop of systolic blood pressure of greater than 20% from baseline or to a systolic pressure of less than 90 mm Hg, was documented and treated with i.v. boluses of ephedrine 6 mg as required. The cardiotocogram (CTG) was recorded continuously throughout the study period. CTG recordings were analysed by one of three obstetric registrars blinded to the treatment groups. The occurrence of late or variable decelerations or fetal bradycardia of less than 110 beats min^{-1} was recorded as significant.

The time to first painless contraction was taken as the onset of analgesia. The duration of analgesia was defined as the interval between intrathecal injection and request for epidural top-up. Quality of analgesia was assessed using a four-point verbal rating score (0 = no pain, pressure or tightening; 1 = aware of tightening or pressure but not painful; 2 = tolerable pain, not distressing; 3 = distressing pain or pressure).

Analgesia assessments were carried out at 5-min intervals throughout the study period. The numbers of recordings of each score were summed from all women in each study group to produce a total for each of the four pain scores. This was then expressed as a percentage of the total number of pain assessments for each study group [cumulative analgesia score (%)].[8] Sensory testing to cold and pinprick was performed at 2-min intervals for the first 20 min and every 5 min thereafter. Vibration sense was assessed with a tuning fork tested at both the knee and the ankle. Proprioception was assessed by testing the joint position sense of the metatarsophalangeal joint of both big toes. Both these functions were tested with the women's eyes closed, at 2-min intervals for the first 20 min and every 5 min thereafter. Motor blockade was assessed using a modified Bromage scale at 5-min intervals (0 = able to straight leg raise against resistance, i.e. no detectable motor block; 1 = unable to straight leg raise but able to flex knee; 2 = unable to flex knee but able to flex ankle; 3 = unable to move hip, knee or ankle). The incidences of itch, nausea and sedation were assessed by direct questioning at 5-min intervals.

Parametric data were analysed using Student's *t*-test and non-parametric data using the Mann–Whitney *U*-test or the χ^2 test as appropriate. For clarity, some data are expressed as a percentage. A *P* value of <0.05 was considered statistically significant.

In a large series of labouring women given analgesia in the form of a CSE, it was demonstrated that 49% of women receiving this 'walking epidural' were unable to straight leg raise against resistance[9] and thus were unable to walk unaided. This figure was confirmed by an assessment of 30 consecutive women receiving a standard bupivacaine CSE in our unit before commencing this study. We found that, in the period immediately immediate after the subarachnoid injection, 43% of the women (13/30) developed demonstrable motor weakness, limiting full ambulation. We felt that it would be clinically significant if the incidence of motor block was reduced to below 10% in the ropivacaine group. The group size of 20 patients in our study gave 85% power to detect this difference.

Results

Forty patients were enrolled in the study. There were no technical problems with the administration of the intrathecal study drugs or the placement of the epidural catheters. All women commencing the study completed the study period successfully and all were included in the subsequent statistical analysis.

No statistical differences were detected between the groups with respect to age, weight, height, gestation, parity or cervical dilatation before analgesia (Table 1). Onset and duration of analgesia are shown in Table 2. The extent of sensory block was similar in the two groups (Table 2). Proprioception was intact in all patients and vibration sense was impaired in one patient in each group. This loss of vibration sense lasted for 35 min in the patient who received

Table 3 Characteristics of block in patients given the drugs shown by intrathecal injection. Numbers of patients, or mean (range). $^*P<0.05$

	Ropivacaine/ fentanyl (n=20)	**Bupivacaine/ fentanyl (n=20)**
Loss of proprioception (n)	0	0
Loss of vibration sense (n)	1	1
Duration of loss of vibration (min)	35	20
Detectable motor block (i e Bromage score >0) (n)	1*	8
Duration of motor block (min)	40	34 (10–70)

Table 4 Maximum degree of motor block seen in patients receiving the drugs shown by intrathecal injection. Motor block measured on Bromage scale (0=full power, able to straight leg raise against resistance, 1=unable to straight leg raise but able to flex knee; 2=unable to flex knee but able to dorsiflex ankle; 3=unable to move leg)

Bromage score (max)	**Ropivacaine/ fentanyl (n=20)**	**Bupivacaine/ fentanyl (n=20)**
0	19	12
1	1	6
2	0	2
3	0	0

ropivacaine and 15 min in the patient who received bupivacaine.

Detectable motor block, i.e. inability to straight leg raise against resistance, occurred in only one patient in the ropivacaine group compared with eight patients in the bupivacaine group and this difference was statistically significant (P=0.019) (Table 3). In the bupivacaine group this motor block lasted for a mean time of 34 min, with a range of 10–70 min. The distribution of maximum motor block seen in each group is shown in Table 4.

Adverse effects were similar in the two groups. Sedation was uncommon. No fetal heart rate abnormalities were detected and no significant maternal hypotension was observed. Itch was frequent in both groups (Table 5).

The majority of pain assessments were either grade 0 or grade 1 in both groups (Table 6), indicating effective analgesia, while scores of 2 or 3 reflected periods of breakthrough pain or inadequate analgesia. The cumulative analgesia score indicates the sum of the number of pain assessments of each score recorded in each patient group expressed as a percentage of the total number of pain assessments. In this way, periods of adequate and inadequate analgesia were related to the total duration of intrathecal analgesia. While more assessments from women receiving bupivacaine were scored as 0 (no awareness of contractions at all), when all assessments of effective analgesia (score 0 or 1) were compared there was no significant difference between the ropivacaine and bupivacaine groups (Table 7).

Twenty-four hours after delivery, all patients reported their analgesia as satisfactory and none reported symptoms of postdural puncture headache.

Table 5 Incidence of adverse effects in patients given the drugs shown by intrathecal injection Values are median (range) where appropriate FHR, fetal heart rate

	Ropivacaine/ fentanyl (n=20)	**Bupivacaine/ fentanyl (n=20)**
Maximum sedation score	0 (0–1)	0 (0–2)
FHR <100/min (n)	0	0
Systolic arterial blood pressure fall of 20% (n)	0	0
Nausea (n)	0	0
Itch (n)	11	11

Table 6 Cumulative analgesia score in patients given the drugs shown by intrathecal injection Pain assessments for each pain score expressed as the percentage of the total pain assessments in each group. No significant difference (P=0 06)

Pain score	**Ropivacaine/ fentanyl (n=20)**	**Bupivacaine/ fentanyl (n=20)**
0	30	49
1	55	37
2	11	10
3	4	4

Discussion

The choice of CSE for labour is advocated as a means of providing rapid, reliable analgesia without significant motor blockade. Indeed, the term 'walking epidural' has been used widely because of the ability of women to remain mobile in labour with this type of pain relief. Collis and colleagues[9] reviewed a series of 300 women receiving CSE analgesia and found 51.3% of the women were able to bear weight and were fully ambulant. Although others were sufficiently mobile to sit in a chair or to be mobile in their bed, almost 13% experienced severe motor weakness that rendered them immobile in the first stage of labour. Considering that this technique aims to offer women the choice of walking safely in labour, there is obviously room for further improvement. As ropivacaine has been reported in several studies to cause less motor blockade than bupivacaine when administered by the epidural route, it was logical to investigate its potential for motor sparing when used intrathecally.

Early studies comparing ropivacaine with bupivacaine for epidural blockade assumed that the drugs were equipotent and compared 0.25% concentrations of both. They demonstrated a tendency towards less leg weakness with ropivacaine, which they attributed to a greater differential block.[10] Alternatively, this could be explained on the basis of reduced potency of ropivacaine compared with bupivacaine. The potency issue has recently been addressed by Polley and colleagues[11] using an up–down sequential allocation design. They have shown that, with regard to analgesia, ropivacaine has a potency 0.6 times that of bupivacaine when given by the epidural route.

Experience of the use of intrathecal ropivacaine is limited. In one volunteer study, McDonald and colleagues,[12] using transcutaneous electrical stimulation

Table 7 Cumulative analgesia scores (%) for effective analgesia (score 0 or 1) and ineffective analgesia (score 2 or 3) for women given the drugs shown by intrathecal injection. No significant difference between groups (P=1.00)

	Ropivacaine/ fentanyl (n=20)	**Bupivacaine/ fentanyl (n=20)**
Effective	85	86
Ineffective	15	14

(TES) as a measure of block intensity, found that ropivacaine 12 mg, given by the intrathecal route, produced tolerance of TES at the ankle similar to that given by bupivacaine 8 mg. Ropivacaine 8 mg did not produce any tolerance to TES and the authors concluded that ropivacaine was less potent than bupivacaine to such a degree that its use for providing spinal anaesthesia was questionable.

In contrast, two clinical studies investigating the use of intrathecal ropivacaine found effective surgical anaesthesia with 15 and 22.5 mg[5,6] without major adverse effects. Although these studies are reassuring with respect to the safety of ropivacaine by intrathecal injection, it is impossible to extrapolate from their results to intrathecal labour analgesia, in which much smaller doses of drug are used.

Little has been published on the use of ropivacaine for intrathecal labour analgesia. Levin and colleagues[7] compared two doses of ropivacaine (2 and 4 mg) with bupivacaine 2.5 mg in a CSE technique and found no difference in duration or quality of analgesia. They also reported no motor block in any of the women, including those receiving intrathecal bupivacaine. This is in contrast to the findings of other researchers[9] and may possibly be explained by the smaller numbers involved (10 per group). The opioid used in conjunction with the local anaesthetic was sufentanil and the ropivacaine dose was chosen on the basis of ease of administration (1 and 2 ml of 0.2% solution respectively) rather than on the basis of potency. We compared equal doses of local anaesthetic (2.5 mg in both groups) and combined this with fentanyl 0.025 mg, as is current practice in our unit. We chose motor power retention as a major end-point and considered a reduction in the number of women with detectable motor blockade to less than 10% as clinically relevant.

We found that both bupivacaine 2.5 mg and ropivacaine 2.5 mg with fentanyl 0.025 mg by intrathecal injection (2 ml) provided effective labour analgesia with rapid onset and duration, similar to the findings of other workers.[3,7] The nature and frequency of side-effects seen in both groups were similar to those reported elsewhere.[3,7,13]

Our most significant finding was the difference in detectable motor block between the two groups. Only one patient in the ropivacaine group developed leg weakness compared with eight in the bupivacaine group (P=0.019). As mobility has been a major consideration in the development and popularity of CSE analgesia in labour, this finding may have important clinical implications. It is not clear if this is due to an intrinsic property of ropivacaine or to a difference in potency between ropivacaine and bupivacaine. Further dose-finding studies would be required to answer this question.

In the past, the safety of ambulation in labour without intact dorsal column function and proprioception was questioned,[14] with implications for allowing women to mobilize freely after CSE analgesia. Recently, however, minimal change in balance function has been demonstrated following CSE analgesia, even in the presence of clinical dorsal column sensory loss [4]. In that study, the only women unable to complete posturography testing were those exhibiting overt motor weakness. This is reassuring in terms of allowing women to mobilize after intrathecal analgesia in labour, but also further emphasizes the importance of minimizing motor block. In this context, our finding of reduced leg weakness using ropivacaine may have significant clinical importance.

Quality of analgesia in this study was assessed on a verbal rating scale by the women themselves at 5-min intervals throughout the study period. Cumulative analgesia scores have been used in other published work to assess analgesic efficacy with both epidural[8] and intrathecal[15] techniques. The benefit of this scoring method is that any periods of inadequate analgesia or breakthrough pain documented are related to the duration of the labour or study period. More pain assessments in the bupivacaine group were grade 0 (unaware of contractions), while more assessments in the ropivacaine group were grade 1 (awareness of tightening or pressure but not pain). This is hardly unexpected, given the difference in potency between the drugs involved. However, when those experiencing effective analgesia (grade 0 or 1) were compared with those experiencing inadequate analgesia (grade 2 or 3) there was no significant difference between the ropivacaine and bupivacaine groups. This is reflected by the fact that all women in both groups reported satisfaction with their analgesia for labour when questioned 24 h after delivery. Indeed, several women in the ropivacaine group commented positively on their ability to feel the contractions without any pain.

We found a similar duration of analgesia in the two groups. Duration is influenced by a number of factors distinct from potency, including systemic uptake and elimination, and in this respect the two drugs appear to be quite well matched. The fentanyl used in the intrathecal injection will also have an effect on the duration of analgesia. However, as the same dose (0.025 mg) was used in the two groups we would still expect any difference in duration due to intrinsic properties of the local anaesthetic to be demonstrated.

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Spinal anaesthesia with 0.5% hyperbaric bupivacaine in elderly patients: effects of duration spent in the sitting position

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Sixty patients, aged 65–84 yr, undergoing minor urological surgery under spinal anaesthesia remained sitting for 2 (group 1, n=15), 5 (group 2, n=15), 10 (group 3, n=15), or 20 (group 4, n=15) min after completion of the subarachnoid administration of 3 ml of a 0.5% hyperbaric bupivacaine solution. They were then placed in the supine position. Analgesia levels were assessed bilaterally using pinprick. Motor block was scored using a 12-point scale. Systolic and diastolic arterial pressures and heart rate were also recorded. Twenty minutes after the injection the upper analgesia levels were lower (P<0.05) in group 4 (median T9.0) than in the groups 1–3 (medians T6.6–T8.5). The highest obtained levels (medians T5.7–T8.0) did not differ between the groups, but occurred later (P<0.05) in group 4 (median 35 min) than in groups 1–3 (medians 19–24 min). There were no significant differences in the maximum degree of motor block or haemodynamic changes between the four study groups.

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Clinical studies have shown that the characteristics of neural block after subarachnoid administration of hyperbaric bupivacaine change with increasing age.[1–3] In particular, the level of analgesia extends approximately three to four segments higher in elderly compared with young adult patients. Old age and high levels of analgesia appear to be the two main factors associated with the development of hypotension during spinal anaesthesia.[4] The degree of hypotension correlates with the level of sympathetic block, which is generally two to four segments higher than the level of analgesia.[5] From a clinical point of view, it is, therefore, important to limit the level of sympathetic block. A spinal technique that prevents unnecessary high levels of analgesia and sympathetic block in elderly patients is, therefore, recommended. One of the benefits claimed for hyperbaric solutions is that their spread can be controlled by posture.[6] The position of the patient at the time of injection may affect the direction of subarachnoid distribution, at least initially. There is, however, still discussion about the duration of the sitting period that is needed to limit the spread of analgesia.[7–9]

The present study examined the influence of different periods of sitting, before the patient is placed in the supine horizontal position, on the spread of analgesia following subarachnoid administration of a hyperbaric bupivacaine solution in elderly patients.

Methods

We studied 57 male and three female patients (ASA I–III, age 65–84 yr), undergoing minor urological surgery under spinal anaesthesia. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center and informed consent was obtained from all patients. Patients with diabetes, a history of neurological disease, or coagulopathy were excluded. Patients were randomly allocated to one of the four study groups, which differed with respect to the time during which the patients remained in the sitting position after the spinal injection. A randomization table was made before the start of the study and codes were stored in sealed envelopes, which were opened shortly before the subarachnoid injection.

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Table 1 Patient characteristics. Data are mean (SD) (range) or frequencies, as appropriate

	Group 1 (2 min)	Group 2 (5 min)	Group 3 (10 min)	Group 4 (20 min)
No of patients	15	15	15	15
Age (yr)	74 (4) (67–82)	75 (5) (68–82)	74 (7) (65–84)	77 (5) (66–83)
Weight (kg)	82 (15)	75 (13)	85 (12)	75 (9)
Height (cm)	181 (9)	178 (6)	177 (3)	176 (3)
Gender (F/M)	1/14	1/14	1/14	0/15
ASA status (I/II/III)	3/10/2	5/8/2	3/9/3	3/10/2

Patients were pre-medicated with temazepam 10 mg orally and atropine 0.25 mg i.m., 45 min before the induction of spinal anaesthesia. Before the spinal injection, 500 ml of glucose in saline was administered by rapid i.v. infusion. Dural puncture was performed with the patient in the sitting position by a standard midline approach using a 25-gauge Quincke spinal needle via an 18-gauge introducer. When a free flow of clear cerebrospinal fluid was obtained and after aspiration of 0.2 ml of spinal fluid, 3 ml of 0.5% bupivacaine in 8% glucose (Marcaine Heavy, specific gravity 1.026 at 20°C) was injected at room temperature at a rate of 0.2 ml s^{-1}. Patients remained sitting for 2 (group 1, n=15), 5 (group 2, n=15), 10 (group 3, n=15), or 20 (group 4, n=15) min after completion of the subarachnoid injection. They were then placed in the supine horizontal position.

Analgesia was assessed bilaterally in the anterior axillary line by pinprick using a short beveled 25-gauge needle. Assessments were made every 5 min during the first 30 min after the injection and at 45 and 60 min. Analgesia was defined as inability to detect a sharp pinprick. Motor block of the lower limbs was evaluated by asking the patient to raise the extended leg (flexion of the hip), flex the knee, and flex the ankle. It was rated per joint (0=no, 1=partial, 2=complete motor block). The results obtained in both extremities were added, giving a maximum score of 12 (complete motor block). Assessments of motor block were made immediately after the assessment of the analgesia levels. The time to maximum cephalad spread of analgesia, the highest level of analgesia attained and the maximum degree of motor block were recorded. During the first 20 min, all assessments were made by the anaesthetist who performed the lumbar puncture. Assessments at 30, 45, and 60 min (i.e. when all patients were lying supine) were made by another anaesthetist who was unaware of the period of sitting.

Systemic arterial pressure, measured with an automatic cycling device (Accutor 1, Datascope) and heart rate (HR) (from the electrocardiogram) were monitored before the subarachnoid injection, after induction of spinal anaesthesia, during surgery and in the recovery room at 5-min intervals during the first 30 min, then at 15 min intervals until the patients were returned to the ward. If the systolic arterial pressure (SAP) decreased more than 30% below the pre-anaesthetic value or to less than 90 mm Hg, ephedrine 5 mg was given intravenously. Bradycardia (HR <55 beats min^{-1}) was treated with atropine sulphate 0.25 mg intravenously.

Group sizes were based on a power analysis, which demonstrated that with a variance s^2=3.39 in the upper level of analgesia (as observed in a previous study in elderly patients),[2] 15 patients would be required per group to have an 80% probability of detecting a difference of two segments between group means at the 0.05 level of significance. Data are presented as mean (SD), mean (95% confidence interval), median (95% confidence interval), or frequencies, as appropriate. Medians and the corresponding 95% confidence intervals were corrected for the presence of tied observations.[10] Maximum changes in SAP and HR were analysed using one-way analysis of variance. Changes in analgesia levels, as well as analgesia levels after 20 min, the highest analgesia levels and the times at which maximum analgesia levels and maximum changes in SAP and HR were reached were analysed with the Kruskal–Wallis test, followed by the non-parametric Student Newman–Keuls test,[10] when indicated. Multiple Fisher exact tests were used to compare the numbers of patients with a complete motor block, and the numbers of patients requiring ephedrine or atropine. To adjust for multiple comparisons in these tests, the sequentially rejective Bonferroni–Holm method was applied. A $P<0.05$ was considered significant.

Results

Patient characteristics are presented in Table 1. Neural block characteristics are summarized in Table 2. In all patients symmetrical analgesia levels were obtained. Median upper analgesia levels *vs* time are presented in Figure 1. The increase in the upper analgesia level after placing the patient in the supine position was similar in groups 1–3, but smaller in group 4 ($P<0.05$). Twenty minutes after injection, the upper levels were lower in patients from group 4 than in patients from the other groups ($P<0.05$; Fig. 2, Table 2). However, the increase in the upper analgesia levels beyond 20 min was larger in group 4 than in the groups 1–3 ($P<0.05$). Consequently, the highest recorded analgesia levels did not differ between the groups, but were reached later in group 4 ($P<0.05$; Fig. 3, Table 2). The number of patients with complete motor block did not differ between the groups.

Table 2 Neural block characteristics. Analgesia data are median (95% confidence interval); motor block data are frequencies (%). ‡Data in group 1 are increases after 5 min (analgesia levels were not assessed at 2 min) *$P<0.05$ compared with groups 1, 2, and 3, †$P<0.05$ compared with group 1

	Group 1 (2 min) (*n*=15)	Group 2 (5 min) (*n*=15)	Group 3 (10 min) (*n*=15)	Group 4 (20 min) (*n*=15)
Analgesia				
Increase after supine positioning (dermatomes)	4.3‡ (2.5–6.5)	4.5 (3.3–8.0)	4.0 (1.0–7.0)	2.0* (1.2–2.8)
Level after 20 min (dermatome)	T6.6 (T7.5–T6.0)	T7.5 (T9.4–T5.0)	T8.5 (T10.5–T4.8)	T9.0* (T11.7–T7.7)
Increase after 20 min (dermatomes)	1.3 (0.6–1.9)	0.8 (0.3–1.5)	1.0 (0.4–2.2)	2.0* (1.2–2.8)
Highest level (dermatome)	T5.7 (T7.0–T5.1)	T7.0 (T8.7–T5.0)	T7.0 (T9.0–T4.0)	T8.0 (T9.3–T6.5)
Time to highest level (min)	24 (18–28)	19† (16–24)	21 (15–24)	35* (25–41)
Motor block				
Patients with complete block (%)	13 (87)	12 (80)	11 (73)	9 (60)

Analgesia was adequate for surgery in all patients. Changes in SAP and HR were similar in all groups (Table 3). One patient in group 2 and four patients in group 3 required ephedrine for treatment of hypotension and one patient in each of the groups required atropine for bradycardia.

Discussion

The present study showed that a 20-min period of sitting is not sufficient to restrict the maximum cephalad spread of sensory analgesia when using 3 ml of 0.5% bupivacaine in 8% glucose. The period of sitting (2–20 min) after a subarachnoid injection of a hyperbaric bupivacaine solution appears to have little, if any, influence on the ultimately attained analgesia levels in elderly patients. This suggests that upward spread of local anaesthetic via the cerebrospinal fluid occurs when the patient is repositioned from the sitting to the supine position, even after prolonged periods of sitting.

With shorter periods of sitting (≤10 min), the upper analgesia level increased by approximately four segments after placing the patient in the supine position. With a longer period of sitting, for example 20 min, the average increase was only two segments. This suggests that with time less local anaesthetic is available for upward spread. This presumably is the result of binding of local anaesthetic to tissue structures within the subarachnoid space, in particular spinal cord.

The effect of the period of sitting on the spread of sensory block following subarachnoid administration of a hyperbaric anaesthetic solution has been studied previously by Povey and colleagues.[7] Their study showed that, irrespective of the period of sitting (2–25 min), analgesia levels increased several segments after the patient had been put into the supine position. Subsequent positioning in a 15° head-down position resulted in a further increase of the analgesia levels by approximately two to three segments. On the other hand, Sinclair and colleagues[11] reported that a 15° head-down tilt had minimal effect on the cephalad spread of analgesia. In that study, however, patients were positioned in the head-down position immediately after the injection and were maintained in that position for only 10 min before being placed into the supine horizontal position. Taken together, the observations of both Povey and

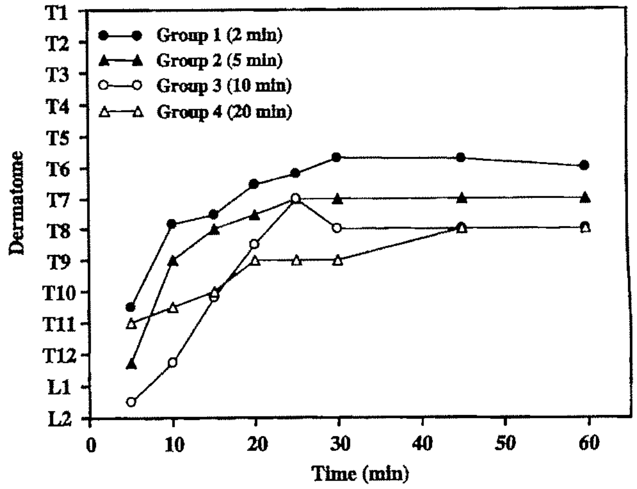

Fig 1 Median upper analgesia levels *vs* time in the four study groups. Medians are corrected for tied observations

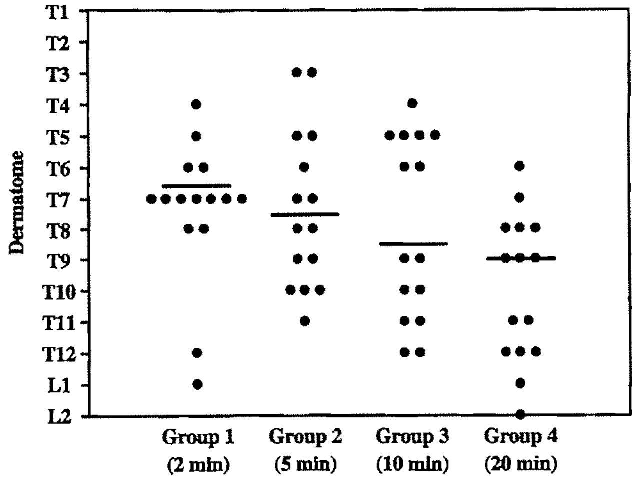

Fig 2 Individual analgesia levels 20 min after the injection. Horizontal lines represent median levels. Medians are corrected for tied observations

colleagues and Sinclair and colleagues suggest that the ultimately achieved upper analgesia level is mainly dependent upon the final position of the patient. This is further substantiated by another study of Povey and colleagues,[8] which showed that sensory block following injection of a hyperbaric bupivacaine solution may still extend rostrally if the patient is placed supine after sitting for as long as 60 min after subarachnoid injection. This indicates that the 'fixation time' of a hyperbaric solution takes at least 60 min with bupivacaine. In both studies of Povey and colleagues, the increase in the highest level of analgesia was considerably larger than in our study. In part, this may be related to differences in the dose of bupivacaine administered, which amounted to 3 ml of 0.5% bupivacaine in this study and 4 ml of 0.5% bupivacaine in the studies of Povey and colleagues.

Similarly, it has been demonstrated that changes in position can alter the spread of sensory block for at least 1 h following subarachnoid administration of a hypobaric lidocaine solution for perirectal surgery.[12] Dermatomal levels remained low (T11–L5) while the patients were in the prone (jackknife) position with the head down at 15° from horizontal, but increased two to six dermatomes if the patient was placed in a sitting position in the recovery room after surgery.

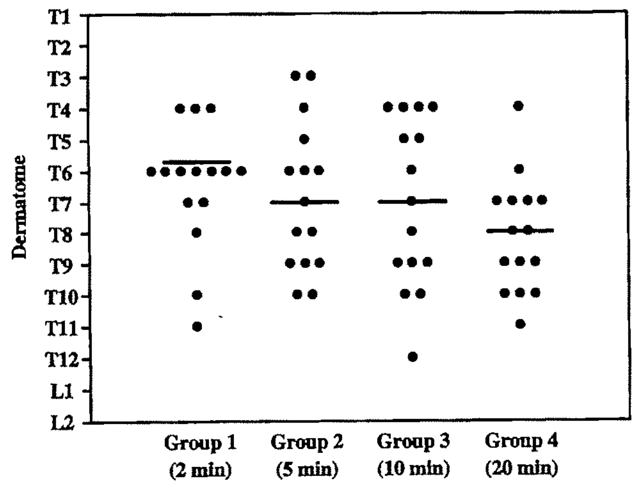

Fig 3 Individual highest levels of analgesia. Horizontal lines represent median levels. Medians are corrected for tied observations.

Positional changes may also extend the sensory block after subarachnoid administration of glucose-free bupivacaine which is slightly hypobaric at body temperature.[13] The level of sensory block increased up to four segments when the patient was placed 30° head up after lying supine for 80–115 min after the injection of glucose-free bupivacaine. This is probably related to migration of unbound bupivacaine within cerebral spinal fluid (CSF). If a true isobaric solution is injected, the epicentre of the local anaesthetic concentration in CSF remains at the site of injection regardless of the position of the patient during and after the injection. This was demonstrated clinically by Wildsmith and colleagues, who studied the effects of posture on the spread of isobaric tetracaine and concluded that posture should not be used to control the spread of isobaric solutions.[9]

Several studies have shown that analgesia levels obtained after subarachnoid injection of a hyperbaric local anaesthetic solution are approximately three to four spinal segments higher in elderly compared with young adult patients.[1–3] The same presumably holds for levels of sympathetic block that are associated with analgesia levels, but are generally two to four segments higher. Consequently, the highest levels of sympathetic block are often in the upper thoracic region in elderly patients, which may explain the higher frequency of cardiovascular side effects in elderly compared with young adult patients.[4 5] Factors that contribute to the more extensive block in the elderly include gradual degeneration of the central and peripheral nervous system,[14 15] changes in the anatomical configuration of the lumbar and thoracic spine,[16] and possibly a reduction in the volume of the cerebrospinal fluid.[6]

Recently, we demonstrated that injecting hyperbaric bupivacaine at a lower (L4–L5) than the usual (L3–L4) lumbar interspace did not reduce cephalad spread of local anaesthetic and did not limit the highest analgesia levels.[17] In that study, as well in this study, there was a considerable inter-individual variation in the highest level of analgesia. These observations are in keeping with earlier reports on the spread of analgesia following subarachnoid administration of hyperbaric bupivacaine, in particular in elderly patients.[2 3] Because of this profound inter-individual variability, the predictability of the analgesia levels that will be reached in an individual patient is low.[2 3 17]

Table 3 Haemodynamic changes and ephedrine and atropine requirements. †Data are mean (95% confidence interval); ‡data are median (95% confidence interval)

	Group 1 (2 min) (*n*=15)	**Group 2 (5 min)** (*n*=15)	**Group 3 (10 min)** (*n*=15)	**Group 4 (20 min)** (*n*=15)
Maximum decrease in SAP (%)†	20 (13–27)	20 (15–25)	21 (14–28)	13 (8–18)
Time to maximum decrease in SAP (min)‡	30 (20–47)	35 (23–47)	28 (20–40)	33 (18–43)
Maximum decrease in HR (%)†	15 (10–21)	18 (14–23)	15 (10–21)	15 (12–18)
Time to maximum decrease in SAP (min)‡	25 (13–40)	47 (25–54)	36 (23–53)	47 (20–54)
Patients requiring ephedrine (%)	0 (0)	1 (7)	4 (27)	0 (0)
Patients requiring atropine (%)	1 (7)	1 (7)	1 (7)	1 (7)

In conclusion, this study has demonstrated that during spinal anaesthesia with a hyperbaric bupivacaine solution the period of sitting has little, if any, influence on final analgesia levels and on haemodynamic changes in elderly patients. These results suggest that the use of posture does not allow as much control over the spread of a hyperbaric solution as is thought.

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Intrathecal ropivacaine for total hip arthroplasty: double-blind comparative study with isobaric 7.5 mg ml^{-1} and 10 mg ml^{-1} solutions

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This study was designed to evaluate the efficacy and safety of two concentrations of intrathecal ropivacaine, 7.5 and 10 mg ml^{-1}, in patients undergoing total hip arthroplasty. One hundred and four patients, ASA I–III, were randomized to receive an intrathecal injection of one of two concentrations of isobaric ropivacaine. Group 1 (n=51) received 2.5 ml of 7.5 mg ml^{-1} ropivacaine (18.75 mg). Group 2 (n=53) received 2.5 ml of 10 mg ml^{-1} ropivacaine (25 mg). The onset and offset of sensory block at dermatome level T10, maximum upper and lower spread of sensory block and the onset, intensity and duration of motor block were recorded, as were safety data. Onset of motor and sensory block was rapid with no significant differences between the two groups. The median time of onset of sensory block at the T10 dermatome was 2 min (range 1–25 min) in Group 1 and 2 min (range 1–21 min) in Group 2. The median duration of sensory block at the T10 dermatome was 3.0 h (range 0.5–4.2 h) in Group 1 and 3.4 h (1.1–5.9 h) in Group 2 (P=0.002). The median duration of complete motor block was significantly prolonged (P<0.05) in Group 2 compared with Group 1 (1.9 *vs* 1.2 h, respectively). Anaesthetic conditions were excellent in all but one patient. Intrathecal ropivacaine, in doses of 18.75 and 25 mg, was well tolerated and provided effective anaesthesia for total hip arthroplasty.

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Ropivacaine, a relatively new amide local anaesthetic with similar local anaesthetic properties as bupivacaine,[1 2] is the first single-enantiomer local anaesthetic to be produced commercially. Although a large number of studies have now been performed using ropivacaine for local infiltration, epidural and peripheral nerve block, clinical data concerning the characteristics of ropivacaine following intrathecal injection are limited. Animal studies have demonstrated that intrathecal ropivacaine has little effect on spinal cord blood flow[3] and that it produces similar sensory block to that of an equivalent dose of bupivacaine, with a reduced degree of motor block.[4]

Although several studies have examined the effects of intrathecal ropivacaine in both labouring women[5] and patients undergoing minor surgery,[6] no studies have evaluated its use in anaesthesia for major surgery. This study was designed to investigate the safety and efficacy of two concentrations of intrathecal isobaric ropivacaine (7.5 and 10 mg ml^{-1}) in patients undergoing primary total hip arthroplasty.

Methods

A Clinical Trials Exemption Certificate was obtained from the Medicines Control Agency and approval for this randomized, double-blind study was granted by the Research Ethics Committee of the Queen's University of Belfast. Written informed consent was obtained from 104 patients who fulfilled the following inclusion criteria: undergoing primary unilateral total hip arthroplasty (cemented prosthesis) under intrathecal anaesthesia, ASA I–III, age 18–80 yr, height ≥150 cm and weight 50–100 kg. Patients

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who had contraindications to spinal anaesthesia, allergy to amide local anaesthetics, a significant history of substance abuse, who had participated in clinical trials in the preceding 3 months or had previously been enrolled in this study, had significant derangement of laboratory values and women of child bearing potential were excluded.

Oral pre-medication consisted of diazepam 10 mg and ranitidine 150 mg. Following arrival in the anaesthetic room, i.v. access was established, full non-invasive monitoring applied and the patient placed in the lateral position with the affected hip uppermost. Following skin infiltration with 1% lignocaine, a 20-gauge introducer needle was inserted at the L2/3 or the L3/4 interspace through which a 25-gauge pencil-point needle with its opening uppermost was passed. Correct needle placement was identified by free flow of cerebrospinal fluid and 2.5 ml of study drug was injected. The spinal needle was removed and the patient placed supine to perform the initial assessments. Following completion of the initial assessments and before the commencement of surgery, patients were returned to the lateral position and a continuous i.v. infusion of 1% propofol commenced. The rate of this infusion was adjusted to render the patients drowsy but rousable. Surgery was commenced within 45 min of the administration of the study drug.

The upper and lower spread of sensory block was determined bilaterally using loss of cold sensation to ice. The dermatomes were identified by reference to a standard diagram. Sensory block was assessed at 2 and 5 min post-injection and at 5-min intervals thereafter until two consecutive levels of sensory block were identical. Assessments were continued at 30-min intervals following the completion of surgery until normal sensation returned. The degree of motor block in the non-operative leg was assessed at the same time points as sensory block using a modified Bromage scale (0=no motor block, 1=inability to raise extended legs, 2=inability to flex knees, 3=inability to flex ankle joints). Assessment of motor block ceased once normal motor function returned. Heart rate and arterial pressure were recorded using standard non-invasive techniques/monitors before intrathecal injection and thereafter at 5, 10, 15, 20, 25, 30, 45, and 60 min, then hourly until 8 h post-injection.

The quality of anaesthesia (judged by the anaesthetist), the quality of muscle relaxation (opinion of the surgeon) and the degree of intraoperative comfort (judged by the patient) were recorded as excellent, satisfactory or unsatisfactory. Intraoperative blood loss, the time to first request for post-operative analgesia and the total morphine consumption in the first 24 h following surgery were also noted. Patients were followed up daily for adverse events (defined as any unintended or unfavourable sign, symptom, or disease temporally associated with the use of intrathecal ropivacaine) and serious adverse events (defined as any adverse event which requires a prolonged hospital stay, results in permanent disability or incapacity, is life-threatening or results in death) for the duration of their hospital stay and again by telephone 14–21 days post-surgery.

Table 1 Patient characteristics and duration of surgery (median (range)) No significant differences

Variable	Ropivacaine 7.5 mg ml^{-1} (n=51)	Ropivacaine 10 mg ml^{-1} (n=53)
Age (yr)	64 (41–80)	67 (43–80)
Height (cm)	164 (150–197)	163 (151–182)
Weight (kg)	74 (51–100)	75 (58–95)
Gender (M/F)	25/26	26/27
ASA I/II/III	17/33/1	13/30/1
Duration of surgery (h)	1.1 (0.7–2.3)	1.0 (0.7–1.9)

A difference of 45 min in the duration of sensory block at T10 was taken to be clinically significant. An estimated 22 patients per group were necessary to detect a 45 min difference in the duration of sensory block at T10 with an 80% power, based on a simple unstratified two-sample 95% *t*-based confidence interval for group comparison, under normality assumptions. The Stratified Wilcoxon (mid) rank sum test was used for comparison between the two groups. A *P* value of less than 0.05 was considered statistically significant.

Results

The characteristics of the two groups were comparable in terms of age, height, weight, gender, and ASA classification. There was no significant difference in the duration of surgery (Table 1). Three patients in the ropivacaine 7.5 mg ml^{-1} group were excluded from the clinical efficacy analysis (one with low serum sodium, one with low serum potassium, one inadequate sensory block). The two patients excluded because of abnormal plasma electrolytes had previously had normal values recorded at the pre-operative assessment clinic and results from samples taken on the day of surgery were unavailable at the time of surgery. One patient in the ropivacaine 10 mg ml^{-1} group was also excluded from the clinical efficacy analysis because of chest pain immediately before surgery. All four patients were included in the safety analysis. All patients were able to co-operate fully with the subsequent assessments.

The median time of onset of sensory block at the T10 dermatome was 2 min (range 2–25 min) in the 7.5 mg ml^{-1} group and 2 min (range 2–21 min) in the 10 mg ml^{-1} group. The median duration of sensory block at the T10 dermatome was 3.0 h (range 0.5–4.2 h) in the 7.5 mg ml^{-1} group and 3.4 h (1.1–5.9 h) in the 10 mg ml^{-1} group (P=0.002).

Whilst there was a trend towards a longer duration of sensory block at different dermatome levels in the ropivacaine 10 mg ml^{-1} group, this difference was not statistically significant. The duration of sensory block in each group is shown in Figure 1. There was no significant difference in either the maximum upper or lower spread

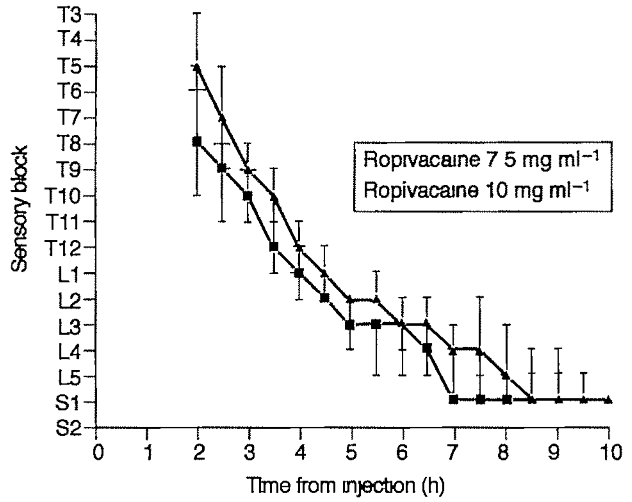


Fig 1 Regression of upper dermatomal level of sensory block with time (median and range) No significant differences

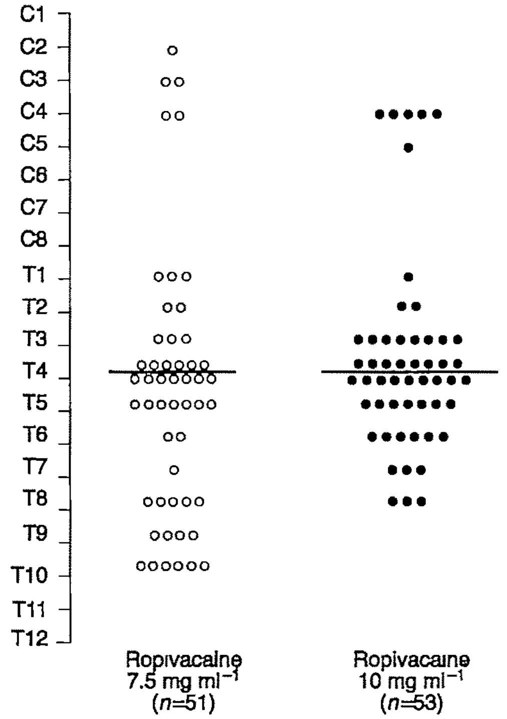


Fig 2 Upper extent of levels of analgesia in the individual patients after intrathecal administration of isobaric 7.5 or 10 mg ml^{-1} ropivacaine. Horizontal bars represent medians No significant differences

of sensory block before or after surgery (Fig. 2). Anaesthesia was judged to be excellent in all patients, except for one in the ropivacaine 7.5 mg ml^{-1} group who complained of deep wound pain approximately 5 min after skin incision despite a pre-operative sensory block to T10. General anaesthesia was instituted, the patient was pain free post-operatively with a sensory block level at T7 and motor block of 3 on the modified Bromage Scale in the recovery ward. This patient had no recall of any intraoperative pain.

All patients achieved motor block of at least 1 on the modified Bromage scale. The onset of motor block was slower than that of sensory block as demonstrated by the increased proportion of patients exhibiting an increased degree of motor block post-operatively compared with the degree of motor block seen pre-operatively. The median duration of complete motor block (modified Bromage Scale 3) was significantly prolonged ($P<0.05$) in the ropivacaine 10 mg ml^{-1} group compared with the ropivacaine 7.5 mg ml^{-1} group (1.9 *vs* 1.2 h, respectively). There were no other significant differences in the degree or duration of motor block between the two groups. The characteristics of post-operative motor block in each group are displayed in Figure 3.

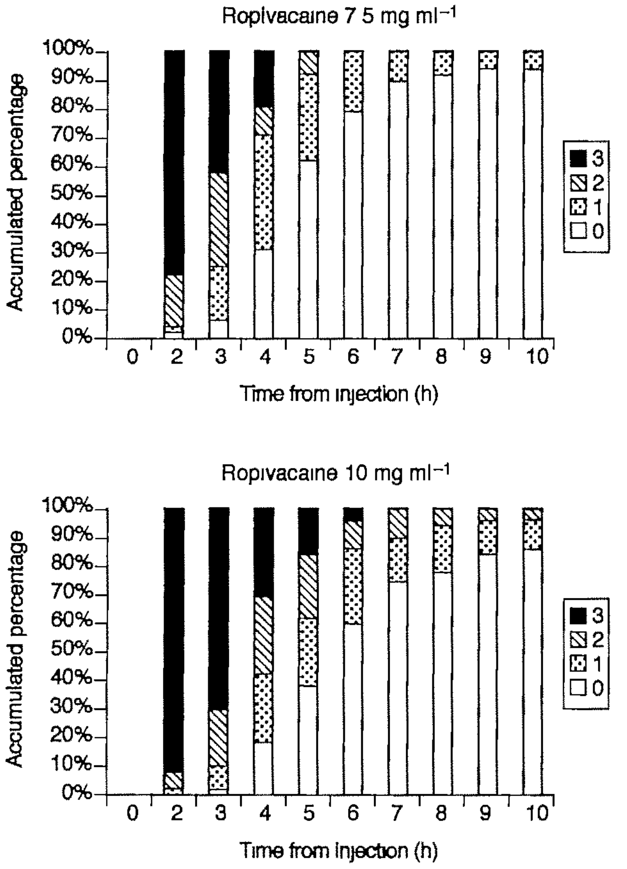
Excellent muscle relaxation was reported in 90% of patients in the ropivacaine 7.5 mg ml^{-1} group and in 98% of patients in the ropivacaine 10 mg ml^{-1} group. All patients reported excellent intraoperative analgesia.

The median time to first analgesic request was similar in both groups (7.5 mg ml^{-1}=3.3 h, 10 mg ml^{-1}=3.9 h). Median morphine requirements (7.5 mg ml^{-1}=50 mg (range 0–94 mg), 10 mg ml^{-1}=42 mg (range 17–120 mg)) in the first 24 h following surgery were similar.

Intrathecal ropivacaine produced an initial moderate decrease in arterial pressure. Intraoperative hypotension requiring treatment with i.v. ephedrine occurred in 24% of patients in both the 7.5 and 10 mg ml^{-1} ropivacaine groups. No patients in the ropivacaine 7.5 mg ml^{-1} group required treatment for intraoperative bradycardia. Three patients in the ropivacaine 10 mg ml^{-1} group required i.v. atropine 0.6 mg to correct symptomatic bradycardia in the intra-operative period. The most commonly reported adverse events during the first 24 h were pyrexia, nausea, vomiting, hypotension, and oliguria. These events were similarly distributed between groups. There was no significant difference in the blood loss between the two groups (median 480 ml in the ropivacaine 7.5 mg ml^{-1} group, median 370 ml in the ropivacaine 10 mg ml^{-1} group).

Discussion

Animal studies have shown that intrathecal ropivacaine produced effective local anaesthesia with an equipotent sensory block but shorter duration of motor block than intrathecal bupivacaine,[4] and no signs of neurological toxic effects have been seen.[3 9] In a study of 40 patients undergoing minor orthopaedic surgery who received 3 ml 0.5% or 0.75% intrathecal ropivacaine, the higher dose was associated with a prolonged duration of analgesia and higher degree of motor block.[6] A crossover study in 18 volunteers who did not undergo surgery, estimated hyperbaric ropivacaine to have a potency of approximately half that of bupivacaine. In this study, intrathecal ropivacaine was associated with a high incidence of back pain.[7] Furthermore, another recent study of 150 patients comparing equal doses of intrathecal bupivacaine with intrathecal ropivacaine in


Ropivacaine 7 5 mg ml^{-1}

Ropivacaine 10 mg ml^{-1}

Fig 3 Motor block following intrathecal administration of isobaric 7.5 or 10 mg ml^{-1} ropivacaine. Numbers represent modified Bromage Scale. Duration of grade 3 motor block significantly prolonged in ropivacaine 10 mg ml^{-1} group (P<0.05)

patients undergoing knee arthroscopy showed a shorter duration of both sensory and motor block with ropivacaine compared with that of bupivacaine. No evidence of post-dural puncture headache or transient radicular irritation was observed in any of the treatment groups.[8]

To our knowledge, this study is the first study to evaluate intrathecal ropivacaine for use as a sole agent in patients undergoing major surgery. The efficacy and safety of two glucose-free solutions of ropivacaine, 7.5 and 10 mg ml^{-1}, were assessed for intrathecal anaesthesia in patients undergoing total hip replacement. Both solutions produced similar results in terms of onset and spread of analgesia. In a previous study which compared 3.0 ml of 5 and 7.5 mg ml^{-1} glucose-free ropivacaine in patients undergoing lower limb surgery, only 32% and 50%, respectively, of patients achieved a sensory block of at least T10.[6] This contrasts with our study in which virtually all patients achieved adequate sensory block. Furthermore, the upper extent of sensory block was much higher in this study with approximately 10% of patients with sensory anaesthesia in the cervical dermatomes compared with a maximum sensory block at the T4 dermatome in the study carried out by van Cleef and colleagues. This may be because of a difference in the characteristics of the populations studied, the use of a higher dose of ropivacaine, or the difference in the position of the patient during the institution of intrathecal anaesthesia. Furthermore, sensory block in our study was tested using loss of sensation to ice rather than loss of sensation to pinprick, which may produce a significant discrepancy in the assessment of sensory block following intrathecal anaesthesia.[10] The subgroup of patients with sensory anaesthesia in the cervical dermatomes did not demonstrate any upper limb motor weakness, respiratory distress, decrease in oxygen saturation, or cardiovascular compromise. This suggests a significant separation in the extent of motor and sensory block when loss of sensation to ice is used.

The one patient in whom a loss of cold sensation to ice at the T10 dermatome did not produce adequate anaesthesia may have had a surgical incision with an upper limit above this level. Furthermore, this patient was pain free in the recovery ward with a sensory level of T7 and motor block of modified Bromage Scale 3 suggesting that the spinal anaesthetic may have had a slow onset.

In common with a previous study,[6] an increase in the dose of intrathecal ropivacaine administered led to an increased duration of profound motor block. The variation in spread of sensory block may be attributed to the use of an isobaric solution.

In terms of safety, both doses of intrathecal ropivacaine provided a high degree of cardiovascular stability with a low incidence of bradycardia. The degree of hypotension was as expected for an elderly population undergoing an operative procedure under a combination of spinal anaesthesia and propofol sedation with an ongoing blood loss; the hypotension seen was associated with the commencement of the i.v. infusion of 1% propofol rather than the institution of spinal anaesthesia. The most commonly reported adverse events were those commonly seen in connection to major surgery.

A significant finding was the absence of symptoms of post-dural puncture headache compared with an incidence of 25% in a previous study.[6] Although spinal anaesthesia was performed using a larger gauge needle in our study (25-gauge as opposed to 26-gauge), the difference in incidence may be accounted for by the use of a pencil-point needle as opposed to a Quinke needle and again by the difference in the age of the two patient groups. This suggests that intrathecal ropivacaine is not associated with an increased incidence of post-dural puncture headache. No patient reported symptoms of neurological problems post-operatively.

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LABORATORY INVESTIGATION

Inhalation anaesthetics increase heart rate by decreasing cardiac vagal activity in dogs

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Inhalation anaesthetics decrease heart rate in isolated hearts but mostly increase heart rate in the intact organism, although most inhibit sympathetic drive. Differences in the degree of increase in heart rate between agents may be related to differences in their vagolytic action. To test this hypothesis, we studied the effects of halothane (H), isoflurane (I), enflurane (E), sevoflurane (S) and desflurane (D) [1–3 MAC (minimum alveolar concentration)] on heart rate and heart rate variability (HRV) as a measure of cardiac vagal activity in seven dogs. HRV was analysed in the time domain as the standard deviation of the RR interval (SDNN) and in the frequency domain as power in the high-frequency (HF, 0.15–0.5 Hz) and low-frequency (LF, 0.04–0.15 Hz) ranges. Heart rate increased with anaesthetic concentration and there were corresponding decreases in SDNN, HF power and LF power. Heart rate increased most with D (+40 beats min^{-1}), least with H (+8 beats min^{-1}) and to an intermediate extent with S, I and E. SDNN and HF power, as measures of vagal activity, changed in the opposite direction and decreased in the same order as heart rate increased. However, SDNN and HF power correlated significantly with heart rate [r=–0.81 (0.04) and –0.81 (0.03) respectively] and were independent of the anaesthetic and its concentration ($P<0.05$). Consistent with our hypothesis, these results suggest that differences between agents in the degree of increase in heart rate are explained by differences in their vagolytic action.

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Inhalation anaesthetics increase heart rate (HR) *in vivo* both in animals[1–3] and humans,[4 5] but decrease heart rate in isolated hearts.[6 7] In the intact organism, HR increases with increasing anaesthetic concentration, i.e. with the depth of anaesthesia but, curiously and for unknown reasons, HR increases more with the halogenated ethers, in particular desflurane, than with the strained-chain hydrogencarbon halothane.[3 4 8 9] Activation of the sympathetic nervous system may explain the increase in HR during desflurane or isoflurane anaesthesia, which has been shown to be associated with increases in spike traffic in sympathetic nerves innervating skeletal muscle in humans.[8–10] This effect, however, is more pronounced during transient than during steady-state conditions.[10] For the other inhalation anaesthetics, this explanation is at variance with the large body of evidence showing inhibition rather than activation of sympathetic drive,[11] particularly at deeper levels of anaesthesia.[12]

Under physiological conditions, HR is determined primarily by cardiac vagal activity,[13] but surprisingly little is known about its response to anaesthesia. Halothane decreases spike traffic in efferent cardiac vagal nerves,[14] but corresponding information is lacking for other inhalation anaesthetics. By the use of HR variability (HRV) as an indicator of cardiac vagal activity, vagal inhibition has also been shown for halothane anaesthesia in dogs and for isoflurane anaesthesia in humans.[15 16] This fragmentary information suggests that cardiac vagal activity may also determine HR during inhalation anaesthesia and that differences between agents in the degree of increase in HR may reflect differences in their vagolytic action. We tested

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this hypothesis in dogs by looking at the effects of five currently used inhalation anaesthetics [1–3 MAC (minimum alveolar concentration)] on HR and HRV as an indicator of cardiac vagal activity.

Methods

The data derive from seven trained dogs (Foxhounds of both sexes, weighing 24–34 kg) studied with approval of the District Governmental Animal Investigation Committee. Each dog received, in random order, each of five anaesthetics [halothane (H), enflurane (E), isoflurane (I), desflurane (D) and sevoflurane (S)], with an interval of at least 1 week between successive experiments in the same animal, so that each dog served as its own control.

Several weeks before the experiments, the dogs were operated under general anaesthesia (enflurane/nitrous oxide+fentanyl) and aseptic conditions. For arterial blood pressure recording and blood sampling, both carotid arteries were exteriorized in skin loops.[17] Ultrasound transit-time flow transducers were implanted around the pulmonary artery through a left-sided thoracotomy for the continuous recording of cardiac output. During convalescence, the dogs were trained to lie quietly and unrestrained on their right side and to become familiar with the experimenters and the laboratory.

The following variables were recorded continuously on an eight-channel polygraph (model RS 3800; Gould, Cleveland, OH, USA) and stored simultaneously on the hard disk of a conventional personal computer for further analysis after analogue-to-digital conversion at the rate of 1000 Hz.

Heart rate and RR interval

HR and RR interval (heart period) were determined from a standard ECG (surface electrodes) that was used for triggering a rate meter, which provided a continuous recording of the RR interval.

Arterial blood pressure

Arterial blood pressure was measured electromanometrically (Statham P-23ID, Elk Grove, USA) through a catheter in the carotid artery. The electromanometer was calibrated with a mercury manometer and referenced to the processus spinosus of the 7th vertebra while the animals were lying on their right side. Mean arterial pressure was measured by integrating the original pressure signal.

Cardiac output

Blood flow through the pulmonary artery was measured continuously with an ultrasound transit-time system (T101; Transonic Systems, Ithaca, NY, USA). Each flow transducer (20–24 mm S-series with silicone-shielded U-reflector; Transonic Systems) was calibrated *in vitro* before implantation and *in vivo* at least 3 weeks after implantation by the Fick principle from oxygen consumption ($\dot{V}_{O_2}$), measured by indirect calorimetry (Deltatrac II®), and the arterial—mixed venous oxygen content difference ($C(\text{a}-\bar{\text{v}})_{O_2}$), measured with a galvanic cell (Lex-O_2-Con-TL, Lexington Instruments, Waltham, USA), giving high precision, as described previously.[18]

Respiratory rate

Respiratory rate was measured continuously with a mercury-in-Silastic gauge mounted around the animal's thorax.

Heart rate variability

HRV, an indicator of the activity of the autonomous nervous system, was studied as described.[19] The original ECG signal, free of aberrant ECG complexes and artefacts, was analysed over a period of 5 min during steady-state conditions after each incremental concentration of the respective inhalation anaesthetic (CHART; ADInstruments, Castle Hill, Australia). HRV was analysed in the time domain and expressed as the standard deviation of the RR interval (SDNN). In addition, HRV was analysed in the frequency domain and calculated as the activity in the high-frequency (HF, 0.15–0.5 Hz) and the low-frequency (LF, 0.04–0.15 Hz) ranges, the former showing exclusively vagal activity and the latter both vagal and sympathetic activity.

During anaesthesia, respiratory gases and vapour concentrations were measured continuously at the endotracheal tube orifice by infrared spectroscopy (Capnomac; Ultima, Datex-Engstrom, Finland). We also intermittently determined arterial blood gas tensions, oxygen saturation and pH (ABL3; Radiometer, Copenhagen, Denmark).

All experiments were carried out with awake dogs in the basal metabolic state (food was withheld for 12 h with free access to water) and under standardized experimental conditions [slightly dimmed laboratory lighting; thermoneutral temperature for dogs (24°C)].[20] During the experiments, which always began at 8 a.m., the dogs remained unrestrained on a cushioned table. To ensure complete elimination of the inhalation anaesthetics, there was an interval of at least 1 week between successive experiments.

After connecting the animals to the recording system, a 30 min stabilization period was commenced. Each experiment began with baseline measurements occupying 30 min, while the awake animals breathed spontaneously. After the insertion of an endotracheal tube (intravenous injection of propofol 3 mg kg^{-1}), the animals' lungs were ventilated with air at a constant rate and, if necessary, tidal volume was adjusted to maintain normocarbia. In the case of desflurane, the vapour was fed together with oxygen-enriched air (30% oxygen in nitrogen) to prevent hypoxia. The anaesthetics were added and immediately adjusted to an end-tidal concentration of 1 MAC (30 min for 1 MAC to minimize

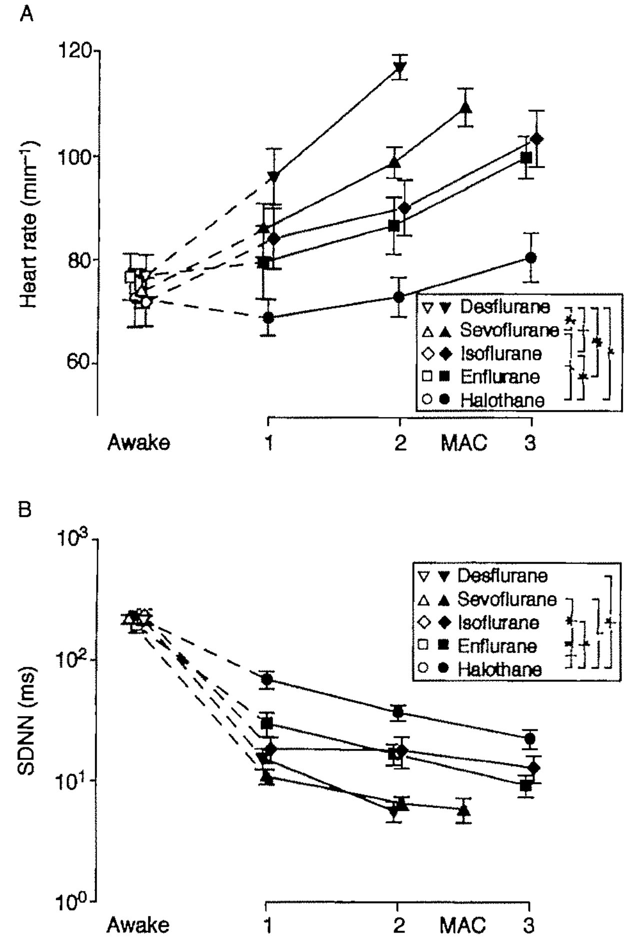

Fig 1 Heart rate (A) and heart rate variability (B) analysed in the time domain (SDNN) during baseline conditions (awake, open symbols) and during anaesthesia with increasing concentrations of five inhalation anaesthetics (closed symbols). Values are mean and SEM for seven dogs Heart rate increased and SDNN decreased with increasing anaesthetic concentration ($P<0.05$); *indicates differences between the anaesthetics.

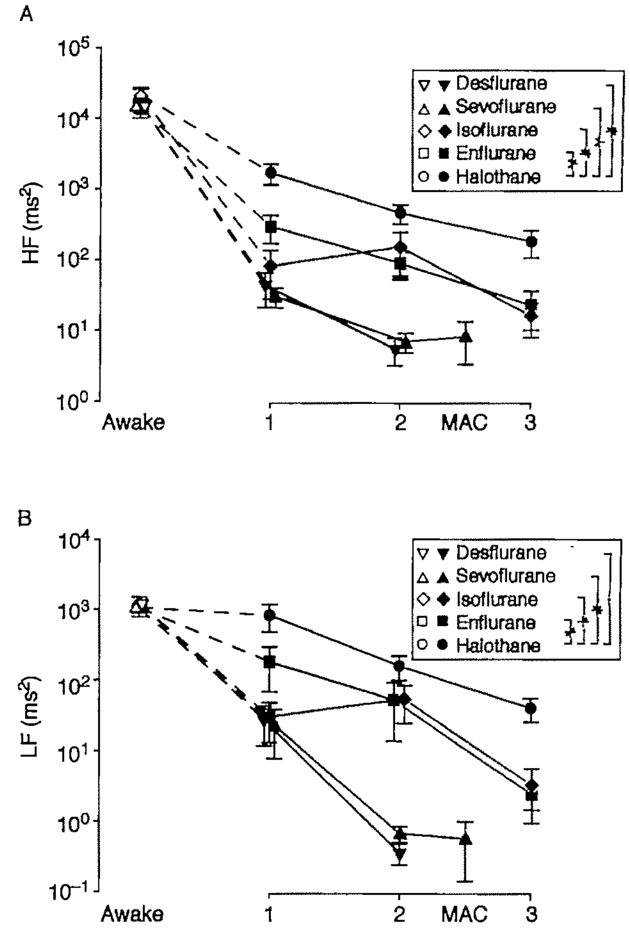

Fig 2 Heart rate variability analysed in the frequency domain [HF (A) and LF (B)] during baseline conditions (awake, open symbols) and during anaesthesia with increasing concentrations of five inhalation anaesthetics (closed symbols). Values are mean and SEM for seven dogs. HF and LF power decreased with the anaesthetic concentration ($P<0.05$) with differences between the anaesthetics. *HF and LF power decreased most during increasing concentrations of sevoflurane and desflurane, and least during halothane anaesthesia.

interaction with propofol) and then to 2 and eventually to 3 MAC (for 20 min). Exposure times were sufficient for the inspiratory and end-tidal concentrations of the anaesthetics to equilibrate.

In addition, we repeated the experiments with D in the presence of β-receptor blockade (propranolol 2 mg kg^{-1} initially, followed by 1 mg kg^{-1} h^{-1}) in two dogs, to exclude the contribution of the sympathetic nervous system to the effects of D on heart rate.

In agreement with the literature, MAC values were assumed to be 0.8, 1.6, 1.4, 2.0 and 7.0 vol% for halothane,[21] enflurane, isoflurane,[22] sevoflurane and desflurane[23] respectively, and the anaesthetics were delivered with conventional vaporizers (Dräger, Lübeck, Germany). Because of limitations of the vaporizers, anaesthetic concentrations had to be restricted to 2.5 and 2.0 MAC for sevoflurane and desflurane respectively.

Results for concentration–effect relationships are given as mean (SEM). Comparisons for heart rate, SDNN and HF and LF power were made by analysis of variance for repeated measures with anaesthetic as between factor. Individual comparisons were made by Fisher's PLSD if appropriate. $P<0.05$ was considered statistically significant.

After logarithmic transformation of the results, linear correlation coefficients were calculated between HRV (SDNN, HF and LF power) and HR for all experiments in one dog and the following null hypothesis was tested: HR during inhalation anaesthesia is independent of vagal activity (SDNN and HF power). For this purpose, the individual correlation coefficients were calculated and compared using a sign test. The null hypothesis was rejected and statistical significance assumed when $P<0.05$.

Results

In general, HR increased and was associated with a decrease in HRV during inhalation anaesthesia. These effects

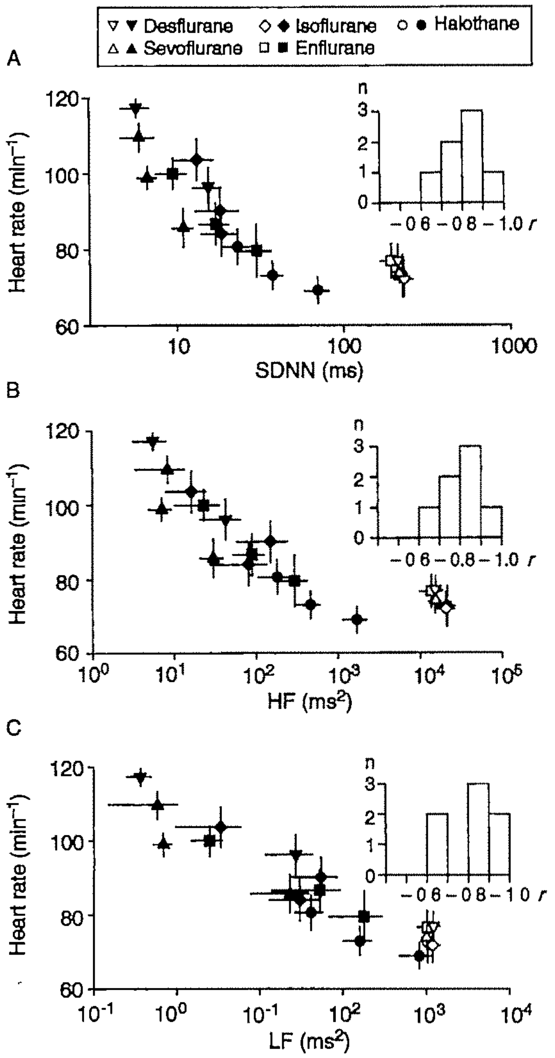

Fig 3 Correlations between heart rate variability [SDNN (A), HF power (B) and LF power (C)] and heart rate for all anaesthetics. Spearman rank correlation coefficients are given in the insets as correlations between heart rate variability and heart rate during anaesthesia (closed symbols) for each individual animal and all anaesthetics Note that the indices of vagal activity (SDNN and HF power) correlated significantly with heart rate ($P<0.05$). Open symbols show the awake values

increased with the concentration of anaesthetic but differed markedly between agents. This is shown by the concentration–effect relationships in Figure 1. At baseline (awake, basal metabolic state), the animals always had a low HR (73–77 beat min^{-1}) with strong HRV (193–230 ms), showing the presence of substantial vagal activity before induction of anaesthesia in all groups. During anaesthesia, HR increased with increasing anaesthetic concentration ($P<0.05$) but, at each MAC, HR changed most with D, less with S, I and E, and least with H. Differences in the degree of increase in HR were substantial; for instance, at 2 MAC the HR was only 73 (4) beats min^{-1} in the presence of H but 117 (2) beats min^{-1} in the presence of D and between the two extremes for the other agents.

These HR changes were always associated with changes in HRV in the opposite direction (Fig. 1B). HRV was already substantially reduced, by about 80%, with the loss of consciousness (i.e. on the transition from awake to 1 MAC), and decreased further to a fraction of the baseline value at ≥2 MAC ($P<0.05$). Note in particular that, at 2 MAC, HRV reached a minimum in the presence of D and S while HRV was about 10 times greater in the presence of H. Thus, the analysis of HRV in the time domain, which mainly reflects cardiac vagal activity, indicates a vagolytic effect and corresponding opposite changes in HR. These effects differed between agents as they were least for H, greatest for D and S and intermediate for E and I.

Similar results were obtained by more detailed analysis of HRV in the frequency domain (Fig. 2). At baseline, HF power was about 10 times greater than LF power, reflecting the predominance of vagal activity in the awake state. During anaesthesia, both indices of the activity of the autonomic nervous system decreased as MAC increased ($P<0.05$); this effect was least for H, greatest for D and S, and intermediate for E and I. Note also the magnitude of these effects: both HF and LF power decreased by about 99% and reached a minimum at 2 MAC for both S and D.

Thus, analysis of HRV showed that the five inhalation anaesthetics inhibited vagal activity in a concentration-related manner. However, these effects differed between agents as at ≥2 MAC vagal activity was strongly reduced in the presence of D and S, less so for E and I, and least for H.

Regardless of these substance-specific differences, HR correlated significantly with the indices of vagal activity during inhalation anaesthesia, independently of the anaesthetic or its concentration (Fig. 3). The correlation coefficients for all experiments in each animal were mostly ≤−0.8 (see inset in Fig. 3). Thus, vagal activity probably determines and regulates HR during inhalation anaesthesia and, accordingly, the substance-specific differences in the degree of increase in HR are related to the level of vagal activity. This interpretation also applies to D, which increased HR even after β-receptor blockade in two dogs from 62 and 74 beats min^{-1} to 114 and 107 beats min^{-1} at 2 MAC in parallel to a reduction in HF power and SDNN by about 99%.

To help in the interpretation of our observations, additional information is summarized in Table 1. Mean arterial blood pressure and cardiac output decreased substantially as MAC increased but there were no differences between anaesthetics. Respiratory rate was essentially the same during baseline in awake animals, and during anaesthesia respiratory rate was maintained for each animal throughout the experiment.

Discussion

We have shown that inhalation anaesthetics elicit a concentration-related increase in HR with a corresponding

Table 1 Haemodynamic variables and gas exchange. MAP=mean arterial pressure. Values are mean (SEM) for seven dogs

Agent	MAC	MAP (mmHg)	Cardiac output (ml kg^{-1} min^{-1})	Respiratory rate (min^{-1})	PCO$_2$ (mmHg)	PO$_2$ (mmHg)	pH
Isoflurane	0	94 (3)	108 (6)	21 (2)	33 (1)	98 (2)	7.39 (0.01)
	1	67 (3)	86 (8)	14 (1)	34 (1)	104 (3)	7.38 (0.01)
	2	46 (3)	64 (8)	14 (1)	34 (1)	104 (4)	7.37 (0.02)
	3	33 (1)	40 (4)	14 (1)	33 (1)	106 (6)	7.38 (0.01)
Desflurane	0	93 (2)	104 (5)	23 (2)	35 (1)	103 (4)	7.38 (0.01)
	1	72 (3)	81 (5)	13 (1)	34 (1)	147 (7)	7.37 (0.02)
	2	54 (5)	58 (7)	13 (1)	36 (1)	143 (4)	7.36 (0.02)
Sevoflurane	0	100 (2)	107 (6)	20 (3)	35 (1)	100 (3)	7.39 (0.01)
	1	69 (3)	75 (7)	13 (1)	34 (1)	96 (1)	7.41 (0.01)
	2	55 (3)	60 (6)	13 (1)	34 (1)	96 (3)	7.40 (0.01)
	2.5	53 (5)	56 (9)	13 (1)	34 (1)	92 (3)	7.41 (0.01)
Halothane	0	95 (2)	101 (5)	20 (1)	34 (1)	107 (4)	7.40 (0.01)
	1	71 (2)	71 (6)	14 (1)	34 (1)	104 (2)	7.39 (0.01)
	2	58 (1)	56 (4)	13 (1)	32 (1)	110 (4)	7.40 (0.02)
	3	40 (2)	35 (4)	12 (1)	34 (2)	106 (5)	7.38 (0.01)
Enflurane	0	103 (1)	107 (9)	22 (2)	35 (1)	106 (4)	7.40 (0.03)
	1	68 (3)	73 (7)	13 (1)	35 (1)	105 (4)	7.38 (0.01)
	2	53 (4)	57 (6)	13 (1)	36 (1)	103 (3)	7.38 (0.01)
	3	40 (3)	40 (4)	14 (1)	34 (1)	105 (5)	7.38 (0.01)

decrease in HRV, but, at equianaesthetic concentrations, these effects differ substantially between agents.

Our conclusions rest primarily on the tenable premise that HRV is a measure of cardiac vagal activity. By definition, cardiac vagal activity is the spike traffic in cardioinhibitory vagal neurones which to date cannot be recorded in the intact organism. As a rule, vagal spike frequency correlates linearly with HR, which, in turn, correlates linearly with the respiratory changes in HR, i.e. the degree of respiratory arrhythmia.[24] The correspondence of these correlations is the rationale for using respiratory changes in HR, expressed as standard deviations, for instance as an index of cardiac vagal activity. This information can be derived simply from continuous recording of beat-to-beat HR (analysis in the time domain). Apart from the vagally mediated HR changes coincident with respiration (respiratory frequency 0.15–0.5 Hz), HR also changes with fluctuations in arterial blood pressure (frequency band 0.05–0.15 Hz), which are associated with changes in sympathetic activity. These two components can be separated by spectral analysis of instantaneous HR (analysis in the frequency domain), and there is agreement that power in the HF band reflects exclusively vagal activity. Power in the LF band, which was primarily thought to reflect only sympathetic activity, has been shown to contain both sympathetic and vagal activity.[19 25 26] Despite these uncertainties, we have included the analysis of the LF range for completeness.

HRV may be influenced by changes in PCO$_2$, respiratory rate and tidal volume.[27 28] Because the influence of tidal volume is small compared with that of respiratory rate,[27 28] the animals were ventilated at the same rate and only tidal volume was varied to maintain normocarbia. Moreover, HRV is strongly reduced by the transition from the awake state (with spontaneous respiration) to anaesthesia (with controlled ventilation).[29] To avoid such interference, we tested only the results obtained during anaesthesia with controlled ventilation. Thus, HRV at respiratory frequencies (activity in the HF range) is a reliable indicator of cardiac vagal activity in our experiments.

The degree of increase in HR differed substantially between the five inhalation anaesthetics. At equianaesthetic concentrations, the increase was greatest for D (40 beats min^{-1}), least for H (8 beats min^{-1}) and intermediate for S, I and E. This essentially confirms previous observations in dogs[1–3] and humans,[5] although the results in humans seem to be less clear at lower concentrations of inhalation anaesthetics.[8 10] Nevertheless, our experiments show for the first time corresponding differences in the strength of vagolytic activity of inhalation anaesthetics.

In contrast to *in vivo* experiments, studies with inhalation anaesthetics uniformly show decreased HR in isolated hearts or isolated pacemaker cells. *In vivo*, they also inhibit sympathetic activity, which would promote decreases—certainly not increases—in HR. At first glance, D seems to be exceptional because it activates specifically sympathetic fibres supplying peripheral blood vessels more during transient conditions than during steady-state conditions.[10] Nevertheless, D evoked greater changes in HR than isoflurane, whereas norepinephrine concentrations did not differ between agents,[30] so that D is not a general stimulant of the sympathetic nervous system. Moreover, although D has been shown to release intramyocardial catecholamines,[31] this agent, like the others, decreased HR in a dose-dependent fashion in isolated hearts.[32] In additional experiments we showed that D produced the same tachycardia even after β-receptor blockade.

Accordingly, during inhalation anaesthesia, cardiac vagal activity is the remainder of the autonomous nervous system participating in the central control of HR. That inhalation anaesthetics inhibit cardiac vagal activity has been shown before for two agents. For instance, halothane decreased both spike traffic in cardioinhibitory neurones[14] and HRV in dogs,[29] as isoflurane does in humans.[15] Our experiments revealed agent-specific differences in the strength of vagolytic action. Regardless of the agent used, the indices of cardiac vagal activity (HRV and HF power) decreased in a dose-related manner, i.e. with the depth of anaesthesia, but the magnitude of this effect increased in the same order as HR increased. At 2 MAC, the indices of cardiac vagal activity decreased to a fraction of the baseline value and had reached a minimum in the presence of either D or S. Vagal activity was still 10 times greater in the presence of H. The corresponding HR was approximately 70 beats $\min^{-1}$ in the case of H but nearly 120 beats $\min^{-1}$ in the case of D. This is the HR that is seen after complete blockade of cardiac vagal activity either by atropine or by cutting the vagal nerves in both dogs and humans.[33 34] The agreement between the drug-specific changes in both HR and the indices of cardiac vagal activity and the close correlation between the two variables (Fig. 3) suggest that, during inhalation anaesthesia, HR depends primarily on cardiac vagal activity. This interpretation is justified because the positive chronotropic effects of the inhalation anaesthetics are unlikely to have been evoked by the accompanying inhibition of sympathetic drive or direct effects on the heart's pacemaker cells.[6 7 35] Thus, our observations support the hypothesis that the differences between inhalation anaesthetics in the degree of increase in HR result from differences in their vagolytic action.

Of note, cardiac output, which has been shown to depend primarily on $\dot{V}_{O_2}$ during inhalation anaesthesia,[36] decreased uniformly in spite of vagally mediated increases in HR.

We cannot explain why, at the same level of anaesthesia, some anaesthetics inhibit the autonomic nervous system more than others. Anaesthetics at high concentrations may stimulate irritant receptors of the airways,[4 37] although the spike traffic from these receptors decreased in a dose-related manner—to the greatest extent for sevoflurane,[38] which is generally accepted as a non-pungent and non-irritating anaesthetic. Accordingly, stimulation of irritant receptors can explain only the transient tachycardia during the induction phase of desflurane anaesthesia, not the continuous increase in HR that occurs at deeper levels of anaesthesia, which are known to suppress any cardiovascular response to manipulation of the airways. It is also unlikely that differences in baroreflex activity would account for the differences in HR between the various inhalation anaesthetics. All suppress baroreflex activity to a similar extent[39–42] and decreased arterial blood pressure to a similar extent in our own experiments.

One limitation of this study is that the autonomic balance in dogs differs from that observed in humans. Whereas vagal activity predominates in the control of HR in dogs, as also shown in this study, the sympathetic nervous system makes a larger contribution than vagal activity in humans.[19] But regardless of these differences, the principle responses of the autonomous nervous system do not differ between the two species. Accordingly, although autonomic balance is not identical in humans and dogs, our conclusions should, with caution, also apply to humans.

HRV reflects the activity of cardioinhibitory neurones in the brainstem. These neurones constitute the final common pathway for all vagally mediated HR changes, not only those of reflex origin via irritant receptors or baroreceptors, for instance, but also those of cortical origin, and hence the state of awareness. It is also of interest that inhalation anaesthetics decrease somatosensory function uniformly, but at the same concentration inhibit the activity of the autonomic nervous system in an agent-specific manner.

Regardless of these general considerations, our experimental findings are consistent with the hypothesis that the differences in the degree of increase in HR between five inhalation anaesthetics are explained by differences in their vagolytic action.

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REVIEW ARTICLE

Structure, conformation, and action of neuromuscular blocking drugs†

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Keywords: neuromuscular block, structure–activity relationship; neuromuscular block, muscle relaxants

Since the introduction of (+)-tubocurarine (dTc),[45] many new neuromuscular blocking (NMB) agents have been brought into anaesthesia practice. The large molecular size and the quaternary ammonium structure of these compounds are unique among anaesthesia-related drugs. For practical purposes, understanding their structure–activity relationship (SAR) is a rational way to understand their actions and metabolism. A 1994 review by Hill and colleagues summarized contributions by previous reviewers and provided details on several series of compounds.[50] Besides molecular structure, this review will cover molecular conformation and attempt to offer explanations.

Historic and scientific background

History

The classic experiments of Claude Bernard led to the recognition of the anatomical gap between motor nerve and skeletal muscle.[7] Dale and colleagues identified acetylcholine (Ach) as the transmitter at the neuromuscular junction.[16 25] dTc was originally thought to be bisquaternary, but in 1970 its structure was revised to correctly indicate that it is monoquaternary.[38 65] The tertiary nitrogen (N) is only protonated, yet dTc nevertheless functions like a bisquaternary compound. Corresponding with the revision, metocurine (mTc) becomes *O,O',N*-trimethyl tubocurarine,[93] instead of *O,O'*-dimethyltubocurarine as it was originally called. It has two permanent quaternary onium heads (Fig. 1).

Hofmann described in 1841 the elimination of an α-β carbon radical from the quaternary N at high pH and temperature (100°C). This is generally called 'Hofmann elimination' (see Stenlake and colleagues[94] for details). In the conception of atracurium, the acyl group was designed to break away under physiological pH and temperature, leaving the tertiary benzylisoquinoline product laudanosine (Fig. 1).

Ach, skeletal muscle endplate AchR, and cholinergic agonists

Ach is a flexible molecule capable of adopting several conformations without significant energy penalty.[23] This allows it to be physiologically multifunctional. Its symmetrical conformers can flip easily. The structure of Ach, CH_3-CO-O-$(CH_2)_2$-$N^+(CH_3)_3$, although simple, has several important functional features, namely the methonium head centred on the positively charged quaternary N atom, the alcohol O atom that forms the ester (-O-), and the acetyl group with the carbonyl O atom (-CO-).

The skeletal muscle endplate Ach receptor (AchR) is generally modelled after the electric organ nicotinic AchR as a pentameric structure of $\alpha_2\beta\gamma$ (or ε) δ subunits arranged in a rosette around a sodium–potassium ionic channel (Fig. 2). Each receptor has two Ach receptive sites, one on each α subunit in a pocket near where the α subunit interfaces with its neighbour γ or δ subunit. Pedersen and Cohen proposed that it is unlikely for the β subunit to be between the α subunits, and accordingly, one likely arrangement of the rosette is αγαβδ, or αγαδβ viewed from the other direction.[58 82 84 92] It takes two Ach molecules acting

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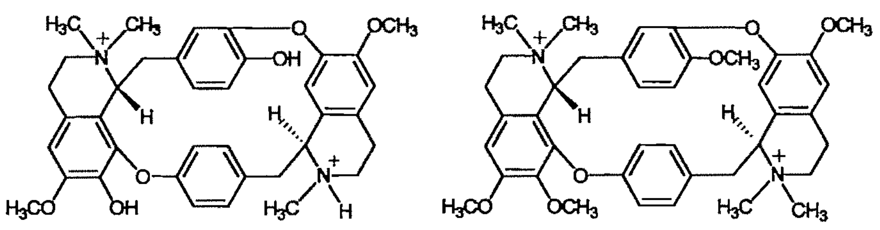
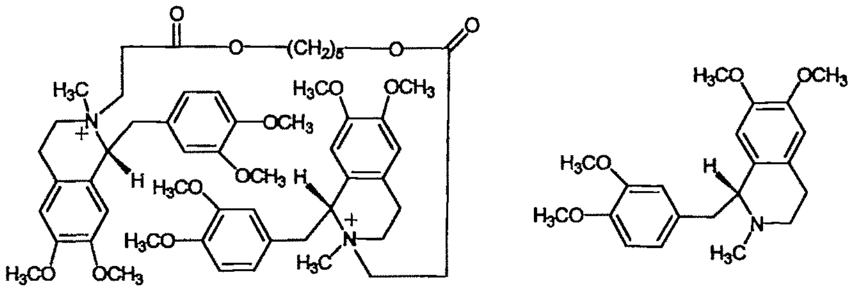


d-Tubocurarine (dTc)

Metocurine (mTc)



Atracurium

Laudanosine

Fig 1 dTc, mTc, atracurium, and laudanosine. Atracurium is drawn in an unusual way of presentation (with the connecting chain around the benzylisoquinolinium heads) to orient its benzyl and tetrahydroisoquinoline moieties with the other compounds. Atracurium is also shown in Figure 6. Removal of the connecting chain of atracurium by Hofmann elimination yields laudanosine

concomitantly, one on each receptive site, to open one AchR channel. The neighbouring subunits make the receptive sites different in affinity. The distance between the two receptive sites has been estimated to be about 50 Å between their outer limits and 30 Å between their inner limits[30 97] (Fig. 2A). The space available for NMB agents could be smaller, but the cross-section of the entire receptor is larger and could exceed 80 Å. The pentameric arrangement in a circle indicates that the two Ach receptive sites are not symmetrical or mirror image to each other (Fig. 2B).

Each receptive site, in turn, has two subsites, namely, an anionic subsite to attract the positively charged onium head and a hydrogen bond donor to attract the hydrogen bond acceptor of Ach (Fig. 2B). The asymmetrical arrangement makes it possible for subsites of like charges to completely avoid facing each other directly.

Various cholinergic receptors and cholinesterases have different conformational requirements or preferences of their agonists (or substrates in the case of cholinesterase) and antagonists. Of the cholinergic compounds, a 1970 report,[4] rarely quoted in literature on neuromuscular pharmacology, proposed that the distance from the centre of the cationic N to the van der Waals (*vdw*) extension of the respective O atom (or equivalent hydrogen bond acceptor) is important in determining whether a cholinergic agonist will be nicotinic or muscarinic (Fig. 3). A distance of 4.4 Å will impart muscarinic action, while a distance of 5.9 Å will impart nicotinic action.[4] For convenience, these two rules will be referred to in this review as the Beers and Reich's rule of 4.4 Å for muscarinic action and rule of 5.9 Å for nicotinic action, respectively. The ester O and the carbonyl O of Ach can fulfil these respective rules readily.

The receptive sites are chiral-sensitive or chiral-selective, if not chiral-specific. For example, cisatracurium is more potent than its stereoisomers supposedly because it fits the receptor at the receptive site better. A conformation of Ach bound to a Torpedo nicotinic receptor has been published.[5] For medicinal chemistry and clinical anaesthesia, however, one must realize that species variation and status of desensitization may alter the conformation of Ach bound to the receptor and/or that of the receptor itself. Free Ach may prefer a bent configuration.[24]

Decamethonium and congeners, and succinylcholine

Pharmacologically, the classic work of Paton and Zaimis established that of the polymethylene bismethonium series of compounds, C5–C12 and C18, congener C10 (decamethonium) is optimal for neuromuscular block.[83] In a biphasic manner, other congeners longer and shorter alike lose NMB potency. Instead of being neuromuscular blockers, C5 and C6 are ganglion blockers. Congeners higher than C11 lose potency, but very long congener such as C18 shows a trend toward re-gaining potency while changing to a non-depolarizing mechanism of block.[50 83]

Chemically, each congener of C10 differs from its neighbour only by one methylene group in the polymethylene chain that connects the two terminal methonium heads. Besides molecular length and a possible slight increment in lipophilicity with each additional methylene

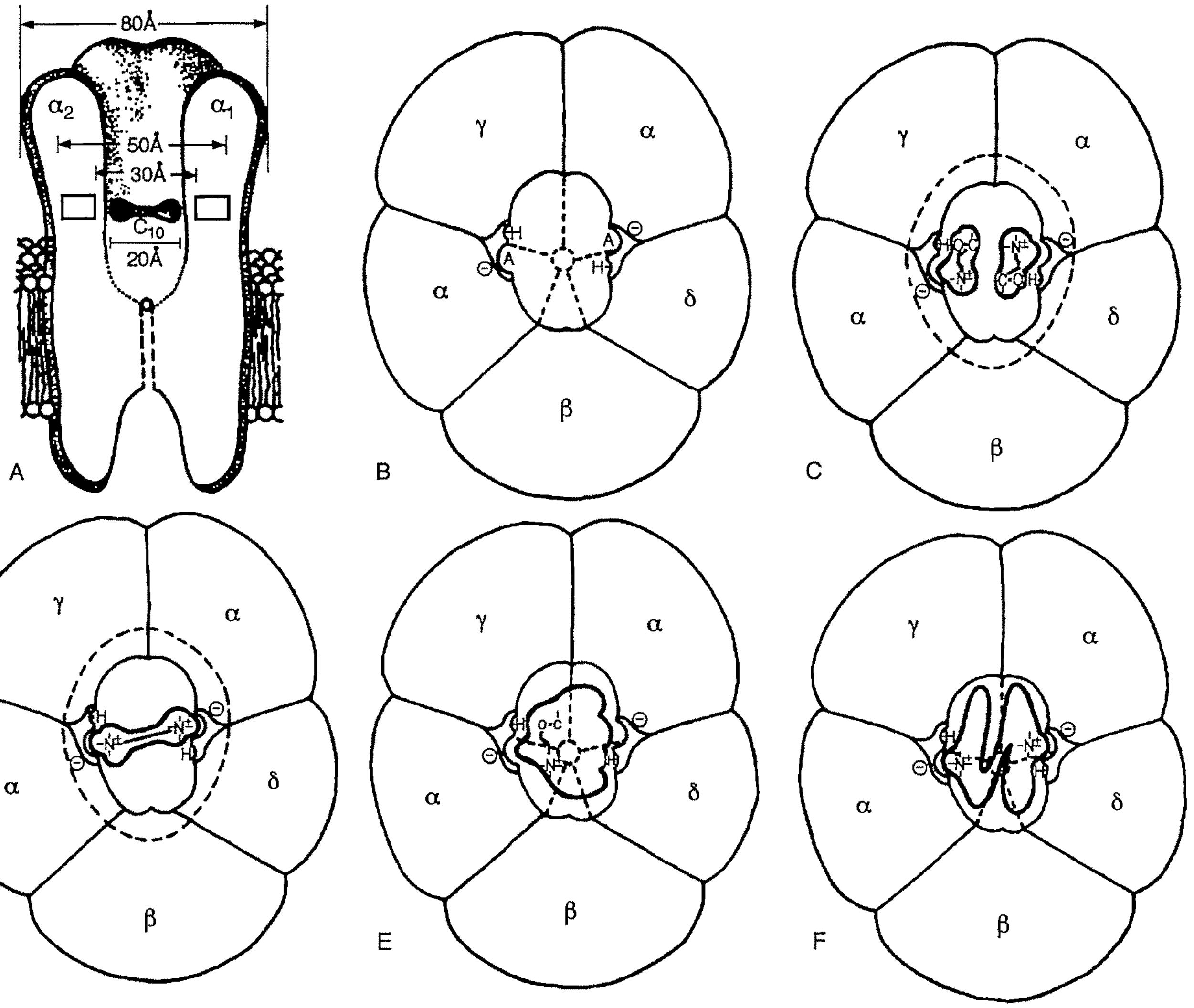


Fig 2 Diagram of a model of the muscle nicotinic AchR, vertical section (A), and cross-section at the level of the receptive sites (B–F) The pentameric rosette is arranged according to one version of Pedersen and Cohen[84] (A) Vertical section showing receptor dimensions and hypothetically a molecule of C10 between the receptive sites. (B) Each receptive site has an anionic subsite (A) and a hydrogen bond donor (H) subsite The circular arrangement maximizes the chances for subsites of unlike charges to face each other and promote closure of the resting channel, shown in dashed lines. (C) Ionic channel opened by two Ach molecules. (D) Ionic channel opened by decamethonium binding both anionic subsites. (E) Blockage by vecuronium (flipped α side up) binding the anionic and the H bond donor subsites of one receptive site. (F) Blockage by a long-chain bisquaternary bulky NMB molecule that bends to fit between the anionic subsites.

group, nothing else explains their different pharmacological profiles. Consequentially, one can assume that at some point of drug–receptor interaction the molecular length of C10 best fits the space available to NMB agents between the two receptive sites of the muscle nicotinic AchR (Fig. 2A and D). However, if the molecule of these congeners may bend to alter its N-N interonium distance with relative ease, such an assumption becomes insecure, and the superior NMB potency of C10 becomes unexplainable.

As is in the case of Ach, it takes two molecules of succinylcholine to open one AchR ionic channel.[30 73] (One wonders whether succinylcholine also exists in bent form and will, therefore, not span the two receptive sites across the channel (see below). Furthermore, if one Ach moiety of succinylcholine binds both the anionic and hydrogen bond donor subsites of one receptive site, its other Ach moiety would be prevented from pointing correctly to the other receptive site.)

Chemical classes and structures of NMB drugs

Ach, succinylcholine, and C10

Ach is the choline ester of acetic acid. Cholines are quaternary ammonium alcohols. Succinylcholine is two Ach molecules joined end-on-end, through the succinic acid connecting chain, $HOOC\text{-}CH_2\text{-}CH_2\text{-}COOH$, a diacid. In C10 congeners, a simple polymethylene chain of various

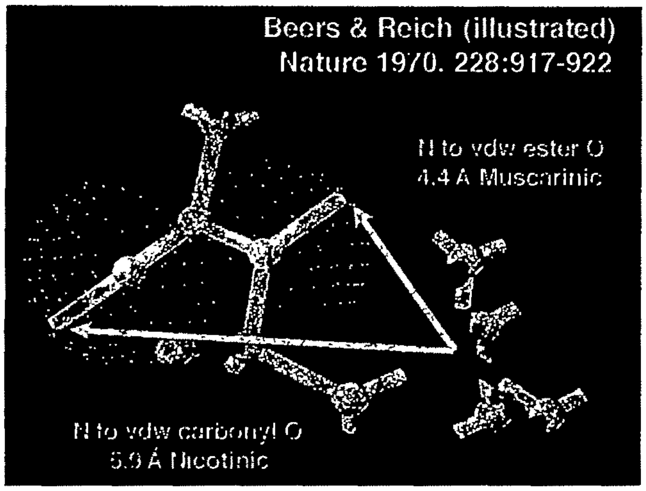


Fig 3 Beers and Reich's rule of 4.4 Å for muscarinic action and rule of 5.9 Å for nicotinic action illustrated together on a hypothetical Ach-like moiety. Red atoms are O, blue atom is N, white atoms are C and green atoms are H. Bars extended out of the O atoms show the direction and length of their *vdw* radii. Arrows point from the centre of N to the *vdw* extension of the O atoms

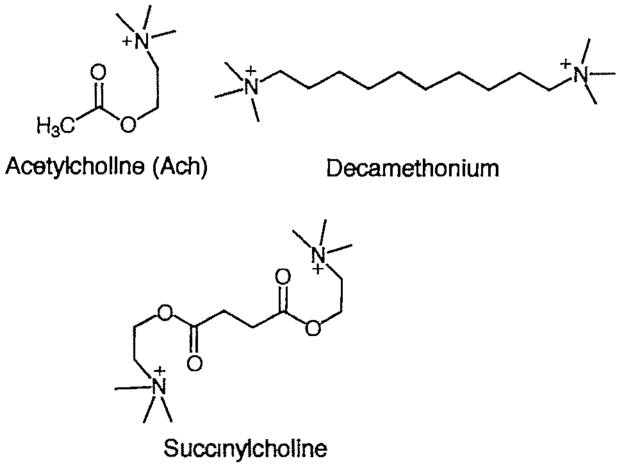


Fig 4 Ach, decamethonium, and succinylcholine. While decamethonium prefers a straight conformation, Ach and succinylcholine prefer bent geometry because of electrostatic interactions between the functional groups (methonium head, carbonyl group and ester O atom).

lengths, -$(CH_2)_n$-, connects the two methonium heads, without any hydrogen bond acceptor (Fig. 4). Although succinylcholine and C10 have the same number of heavy atoms (C, O) between their methonium heads, succinylcholine has complex functional groups and is a shorter molecule. Both succinylcholine and C10 have small trimethyl onium heads and flexible links.

Aminosteroids

Pancuronium, vecuronium, rocuronium, rapacuronium, dacuronium, malouètine, duador, dipyrandium, pipecuronium (Arduan), chandonium (HS-310), HS-342 and other HS- compounds[1 8 28 29 32 37 41–43 62 75 76 80 81 98] are among the aminosteroid NMB agents. The steroid nucleus provides a rigid bulky structural base (Fig. 5). Of the two Ach moieties of pancuronium, the A-ring Ach has *trans* geometry, with the charged N group pointing up (β) while the acetoxy group points down (α). The D-ring Ach has *cis* geometry, with both functional groups pointing up (β). In the case of vecuronium, the A-ring Ach moiety is tertiary, without a methyl quaternizing group. Vecuronium is, therefore, D-ring Ach monoquaternary. Its A-ring Ach is a 'NOR' ('Nitrogen ohne Radical' in German, or nitrogen without radical), as in the trade name (Norcuron®). As pancuronium and vecuronium are roughly equipotent, their NMB action can be attributable to their common *cis* D-ring Ach moiety. Details of conformation–activity relationships (CAR) of the A-ring and D-ring Ach moieties, especially in connection with their different NMB *vs* cardiovagal blocking profiles, are discussed in a separate section below. Strangely, some conformationally rigid small *cis* analogues of Ach are inactive.[21]

Tetrahydroisoquinoline derivatives

Atracurium, mivacurium, and doxacurium are benzylisoquinolinium compounds based on the tetrahydroisoquinoline moiety (Fig. 6).[2 3 6 71] On their benzylisoquinolinium heads are 4, 5, or 6 methoxy groups, in that order. The connecting chain between the two onium heads is long, and flexible except for the double bond of mivacurium. Other benzylisoquinolinium NMB compounds may have rigid segments in their connecting chain.[50] The connecting chain for doxacurium is succinate, although doxacurium is not readily metabolized by plasma cholinesterase. In the case of atracurium, the ester linkage is reversed, meaning that the ester O and the carbonyl groups (CO) are transposed, -CO-O-$(CH_2)_n$-O-OC-, instead of -O-OC-$(CH_2)_n$-CO-O-. By definition, the benzylisoquinolinium structure of atracurium is an acid, not alcohol or choline, and the esters are not cholinester.

On first sight, dTc and mTc do not look like atracurium, mivacurium, or doxacurium. However, they are benzylisoquinolinium compounds. Their onium heads are interconnected by ether linkages between the tetrahydroisoquinolinium group of one benzylisoquinolinium and the benzyl group of the other, instead of by a long diester chain between the quaternary N atoms (Figs 1 and 6).

Gallamine and other chemical classes

Gallamine is a trisquaternary ether, with one ethonium head each attached to the 1, 2, 3 positions of a phenyl ring through an ether linkage -O-$(CH_2)_2$-$N^+(CH_2CH_3)_3$ (Fig. 7).

Many other chemical structures, such as fazadinium (AH8165), alcuronium (alloferin), diadonium, anatruxonium, and tropeinium,[14 15 17 26 27 48 52 53 57 59 88] have been exploited for NMB properties. Some of these illustrate SAR

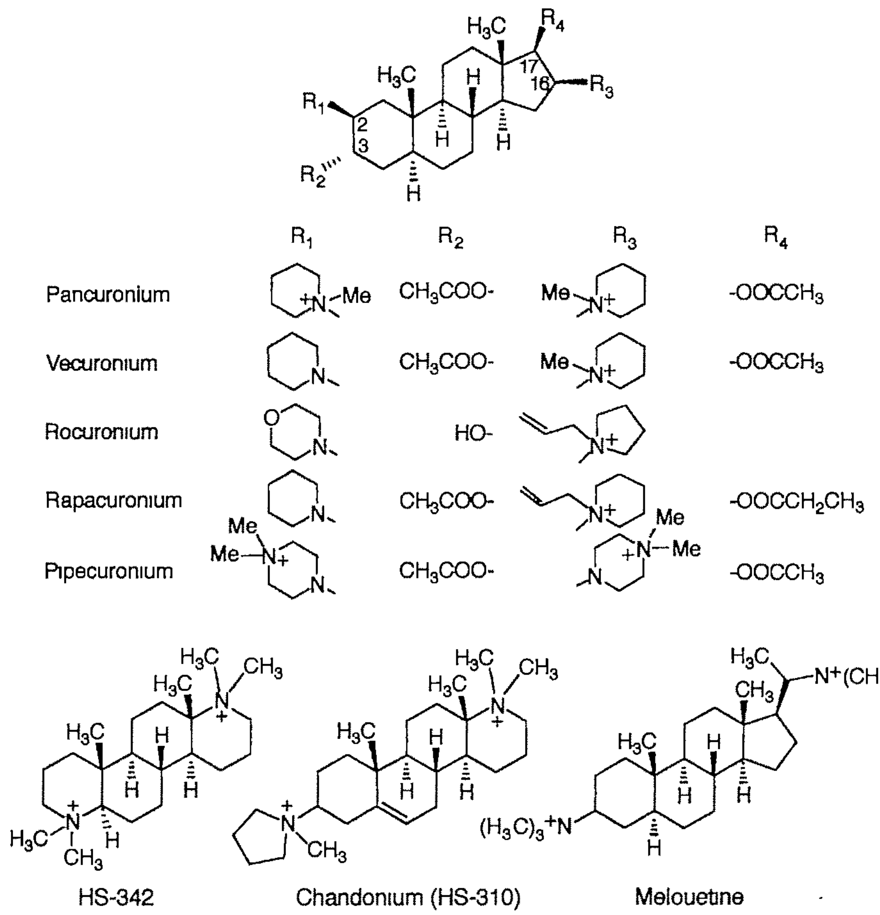
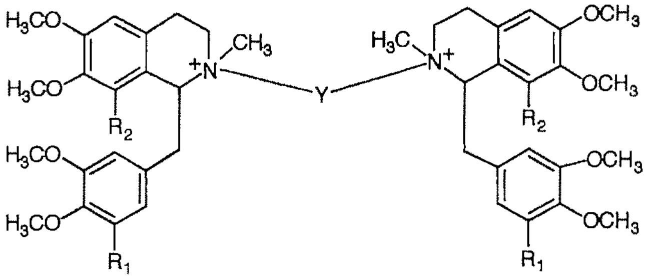


Fig 5 Molecular structures of some aminosteroid NMB agents. The beta (up) surface of the molecule is crowded with, *clockwise*, R1, two methyl groups, R4 and R3. The R1, R3–4 groups are tilted outward sidewise. Longer groups on R3 or R4 replacing the methyl group decrease potency, see text. The quaternary N atoms on pipecuronium are farthest out HS-342, chandonium and malouètine differ, among others, in interonium distance



	Y	R_1	R_2
Atracurium	$-CH_2CH_2CO\text{-}O\text{-}(CH_2)_5\text{-}O\text{-}OCCH_2CH_2-$	-H	-H
Mivacurium	$-(CH_2)_3\text{-}O\text{-}OC(CH_2)_2CH{=}CH(CH_2)_2CO\text{-}O\text{-}(CH_2)_3-$	$-OCH_3$	-H
Doxacurium	$-(CH_2)_3\text{-}O\text{-}OCCH_2CH_2CO\text{-}O\text{-}(CH_2)_3-$	$-OCH_3$	$-OCH_3$

Fig 6 Atracurium, mivacurium and doxacurium have 4, 5, and 6 methoxy groups, respectively, on each of their onium heads and their NMB potency increases in the same order. The connecting chain of atracurium has two reversed esters. The tertiary product of Hofmann elimination from atracurium will be laudanosine.

well (Fig. 8). For more information, refer to individual publications and the reviews by Hill and colleagues, and Kharkevich.[50 62] The review by Kharkevich is a useful liaison to significant works published in Russian.[60 61 63]

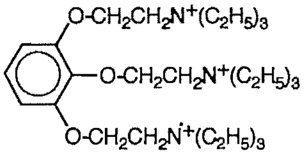
Novel NMB agents

Of timely interest are a new series of asymmetrical diester isoquinolinium compounds[10] and a series of new bisbenzyltropinium compounds (Fig. 9).[46 47] Both were recently introduced as candidates for the earlier defined 'ideal' ultra-fast and ultra-short-acting non-depolarizing NMB agent.[89] The former series of compounds differ from their benzylisoquinolinium predecessors by having asymmetrical structures, such as with one phenyl and one benzyl isoquinolinium head. The connecting diacid chain can also be asymmetrical, such as chlorofumarate (-CO-CH=CCl-CO-). Initial human trials have produced promising results. The latter group, that includes G-1-64, is bistropinium salts of various diacids. The onium head may have a benzyl group that is acyloxylated.[46] They are undergoing extensive pre-human testing (personal information).

SAR

Pachycurares and leptocurares

A rule of SAR that was discovered early on and still seems valid is that bulky and rigid ('pachy' meaning thick) molecules or onium heads usually cause non-depolarizing block, while slender, small and flexible ('lepto' meaning thin) compounds usually result in depolarizing block.[11] Rigidity often co-exists with bulk, as large numbers of atoms form specific ring structures. Methonium is a small onium head and succinic and polymethylene groups are small and flexible links (Fig. 4). They make succinylcholine and C10 depolarizing. The steroid nucleus is bulky and rigid, so are benzylisoquinolinium and tropinium heads, and they are the structural basis of potent non-depolarizing NMB agents (Figs 1 and 5–9).



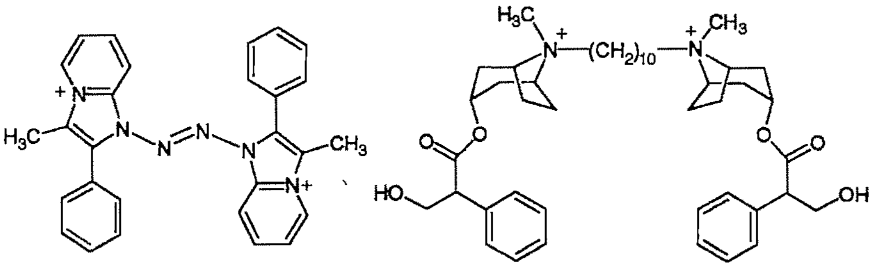
Gallamine

Fig 7 Gallamine is tris-quaternary, with three ethonium heads attached to the phenyl ring through ether links See Figure 10 regarding its CAR.

Tertiary, monoquaternary, bisquaternary, and multiquaternary compounds

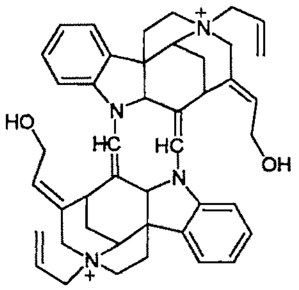
Succinylcholine and C10 are bisquaternary. dTc is monoquaternary, but the tertiary N is protonated. mTc has both its N atoms permanently quaternized and is more potent than dTc.[87 93] Pancuronium was the most potent NMB agent known at the time of its introduction. Of the HS series, bisquaternary compounds are much more potent than their monoquaternary analogues.[43] Before the discovery of vecuronium, these observations were convincing evidence that potent NMB agents, depolarizing or non-depolarizing, must be bisquaternary.

The discovery of vecuronium established the value of some monoquaternary aminosteroids as superior NMB agents (Fig. 5). It has been said that between pancuronium and vecuronium, in the early days of development of the aminosteroid series of NMB agents, pancuronium was



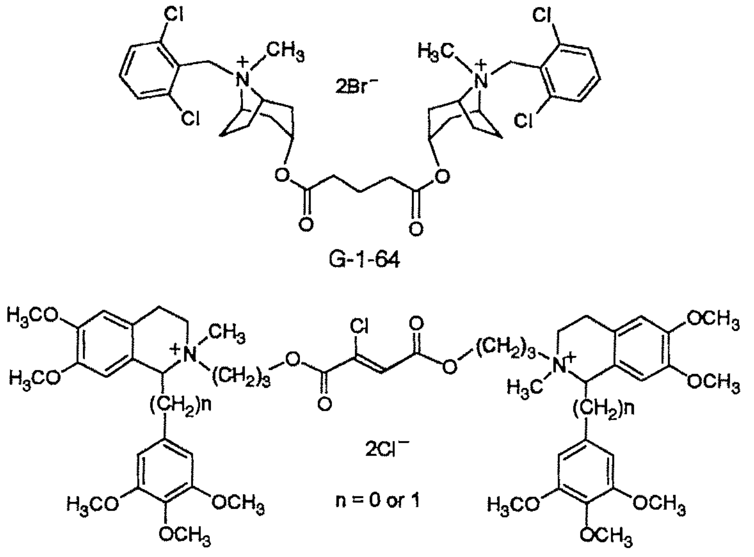
Fazadinium (AH8165)

Decamethylene bisatropine



Alcuronium

Fig 8 Fazadinium has a short interonium distance. Alcuronium has a rigidly fixed interonium distance, but the number of interposing atoms is debatable. Decamethylene bis-atropine consists of two atropine molecules connected by a quaternizing C10 linkage, which rotates only within a narrow range of interonium distance.



G-1-64

Bis- or mixed-tetrahydroisoquinolinium chloroformates

Fig 9 Novel compounds as candidates for ultra-short and ultra-fast-acting NMB agents. G-1-64 is prototype of a large series of benzyl-quaternized bis-tropine diesters, many of which have an acyloxylated benzyl group[46 47] The chlorofumarates can have dissimilar onium heads. Chlorofumaric acid is itself an asymmetrical diacid

developed ahead of vecuronium because of its bisquaternary structure.[33 85] It was also said that Nicholas Durant, then a PhD student, while learning the 'bisquaternary rule', 'accidentally' discovered the superior NMB profile of vecuronium (personal communication).

Gallamine is trisquaternary. There are also tertiary amine NMB agents, and compounds with more than three onium heads.[50 62 74] They are not superior NMB agents, some also producing block pre-junctionally.

Pipecuronium and other aminosteroid NMB agents

The aminosteroids illustrate several important SAR and CAR and these will be discussed under separate headings. Meanwhile, it is noted that pipecuronium is chemically bisquaternary, with dimethylpiperazinium heads on the A and D rings of the steroid nucleus (Fig. 5). Its functional groups are far from being Ach-like in geometry, indicating that pipecuronium probably blocks neuromuscular transmission as a bisquaternary compound (with both onium heads), in contrast with vecuronium and analogues that block with their D-ring Ach moiety as monoquaternary. Pipecuronium matches or exceeds pancuronium in potency.

Separation of the charged quaternary onium heads

Ten heavy (C or O) atoms separate the quaternary N atoms of C10 and succinylcholine (Fig. 4). When two molecules of quaternized atropine (Fig. 8) or other suitable onium heads are interconnected, a polymethylene chain of 10 C atoms imparts greatest NMB potency.[50 62 64] For dTc, mTc, and pancuronium, one can also count 10 atoms along one path or another from one N to the other (Figs 1, 5 and 8). This is the so-called '10-atoms rule' for NMB potency.

Separation of the two quaternary N atoms (by 5–6, 10–12 or 15–18 C atoms) determines the cholinergic (ganglionic *vs* neuromuscular) profile of the congeners of C10.[83] In days past, some concepts were passed down to anaesthesia trainees that cholinergic 'receptors' might be spaced 5-carbon lengths apart, so that potent nicotinic antagonists span 1, 2, or 3 such lengths. This is obsolete because, obviously, receptors are, in fact, much larger (Fig. 2).

The '10-atom rule' of NMB potency is flawed by the fact that the interonium distance maintained by the 10 atoms differs markedly among potent NMB agents. Succinylcholine tends to assume a bent conformation, and is, therefore, shorter than C10 (Fig. 4). The two N atoms in mTc, pancuronium, and alcuronium are not fixed along a straight line. An interonium distance of 14 Å for them is a frequent misquote (Figs 1, 5 and 8). Equally ambiguous is the 15–18-atom interonium distance for the return of NMB potency. The connecting chains of modern long-chain muscle relaxants are too flexible and variable to support the 15–18-atom distance hypothesis (Figs 6 and 9). They may bend to fit the 10-atom distance instead.

It is the linear interonium distance, not the number of interposing atoms, which generally differentiates between NMB and ganglion blocking potencies. C5 and C6, dTc, the bisquaternary HS compounds and AH8165 show that bisquaternary NMB agents with shorter interonium distance are associated with increased ganglionic block.[15 75 93] Conformational details of this are discussed below.

Importance of one methyl substitute on the functional groups for potency

Most potent NMB agents have at least one methyl group on the active quaternary N atom. In place of the methyl group, rocuronium and rapacuronium have a propenyl (-CH_2-$CH=CH_2$) and gallamine has all ethyl quaternizing groups (Figs 5 and 7). As a result, rocuronium and rapacuronium are much weaker than vecuronium.[50 77 90 99] Likewise on the functional hydrogen bond acceptor, acyl groups larger than acetyl also reduce potency. Rapacuronium, the newest aminosteroid NMB agent, has 16-N-propenyl and 17-propionyloxy (CH_3CH_2COO-) groups. For losing both methyl groups, it is more than 10 times weaker than vecuronium.[8 44]

Lipophilicity and the potency of aminosteroid NMB agents

Wierda and colleagues reported that among several aminosteroid compounds, the NMB potency is inversely related to the lipophilicity.[99] One wonders whether this inverse correlation with lipophilicity is an independent determinant of potency or coincidental with other factors, such as steric hindrance.

In general, a 16-N quaternizing group larger than methyl that makes the aminosteroid a weaker NMB agent is also more lipophilic. So is a 17-acyloxy group larger than acetoxy. Conformationally, any group bulkier than the methyl might distance the functional groups from the action centres of the receptor and impose charge dilution and steric hindrance, which in turn reduce NMB potency. Pipecuronium has least hindered and highly hydrophilic onium heads (Fig. 5), and it excels in potency.

Methoxy groups increase potency of benzylisoquinolinium NMB agents and reduce side effects

Both hydroxy groups of dTc are methylated in mTc (Fig. 1). As a result, mTc has four methoxy groups, while dTc has two, and mTc has 2–3-fold greater potency and specificity than dTc.[86 87] Atracurium, mivacurium, and doxacurium have on each of their benzylisoquinolinium heads 4, 5, and 6 methoxy groups, in that order (Fig. 6). Their potency increases in that same order.[2 3] The reduction of histamine release could also be attributed to the increased number of methoxy groups, by improved specificity or indirectly by reduction of dose requirement.

Hydrogen bond acceptor requirement

To be a potent monoquaternary NMB agent, a properly positioned hydrogen bond acceptor must accompany the active onium head. This requirement is observed in the weak non-acyloxylated monoquaternary aminosteroid compounds (including the HS series), and in the 17-desacylated products of vecuronium and analogues.[43 62 75 85 99]

Metabolizable bonds, degradation, and excretion relationships

Molecular structure of most NMB agents relates to their metabolic pathways, although exceptions exist. Even without enzymatic catalysis, short-acting NMB agents, especially the ultra-short ones, may break down spontaneously. The new asymmetrical isoquinolinium[10] and bistropinium diester compounds (personal information) most likely break down spontaneously *in vivo*. These compounds have unusual destabilizing molecular structures, such as molecular asymmetry (Fig. 9) or acyloxy groups around their onium heads (personal information).

As non-cholines, and, therefore, not substrate of any cholinesterase, the reversed ester linkages of atracurium and cisatracurium are made to break down by Hofmann elimination, and/or non-specific (i.e. non-choline) esteratic hydrolysis, both in plasma.[22 39 94] Plasma cholinesterases hydrolyse succinylcholine and mivacurium, but not doxacurium.[40 71] The exception of doxacurium illustrates our incomplete understanding of the structural requirements and quantitative SAR for hydrolysis by plasma cholinesterases.

Esters hydrolyzed by hepatic esterases are usually non-cholines, as the cholinesters are already broken down in the plasma or tissue. In general, very water-soluble NMB agents undergo renal excretion, while the liver takes up less water-soluble ones for metabolism and/or biliary excretion. Among the aminosteroids, the hydroxy products are generally less water-soluble than their parent esters,[32] and pipecuronium is more dependent on the kidneys for excretion than its 16-onium,17-aceloxy analogues.

The ester structures on positions 3 and 17 of the aminosteroid NMB agents are susceptible to hepatic esterases for de-acylation to 3-OH, 17-OH and/or 3,17-dihydroxy metabolites.[9 32] With a steroid link, these pharmacologically Ach-like moieties are chemically distant from Ach. They are, therefore, not substrates for plasma or tissue cholinesterases. Rapacuronium deserves special mention. It is rapidly hydrolyzed to 3-OH rapacuronium, spontaneously or catalysed 'by esterases of unknown identity and site' (quoted from official package insert of Raplon®), not in the liver. As a result, its NMB action is not significantly altered in hepatic failure,[35 96] although its metabolite, (see below), is active and theoretically may be cumulative.

C10 has no metabolizable bonds. Gallamine has three and mTc has two ether (besides methoxy) links. Although ether inhalational anaesthetics are metabolized to some extent, ether NMB agents are hardly metabolized. These agents, as well as doxacurium, are eliminated intact through the kidneys. Methoxy group breakdown or removal is not recognized as a metabolic pathway for NMB agents.

While plasma cholinesterase may be atypical, inhibited or deficient, and hepatic esterases may be deficient in hepatic failure, non-specific esterases have a greater margin of safety and Hofmann elimination or spontaneous breakdown rarely fails under clinical pH or temperature. The above provides the basis for choice of NMB agents in managing patients with organ failures or atypical or inhibited plasma cholinesterases.[20 34 35 54–56]

Structure–onset relationship

Unfortunately, little is known about the independent relationship between structure and onset of NMB action, which so far has only been observed to relate inversely to potency.[12 66 78] Bowman and colleagues made this observation on the aminosteroid compounds,[12] as did Wierda and Proost,[99] and then Nigrovic and colleagues.[79] Kopman and colleagues expanded this observation to include NMB agents of all ranges of duration of action.[66] Being weaker and faster than their predecessors, the new aminosteroids, rocuronium and rapacuronium, are no exceptions.[99] The rapid onset of rocuronium appears to qualify it as an outlier,[37] but not really an exception to the rule considering its relatively low potency.[77] The new asymmetric isoquinolinium compounds appear unusually fast for the potency.[10]

The inversed potency–onset relationship is a disappointment. Potency of action is often determined by specificity of receptor binding. In other words, it is a means towards freedom from side effects. Unfortunately, sacrificing some specificity appears so far to be the only known method to speed up onset of action, as was done in the development of rocuronium and rapacuronium. Rapacuronium incurs more side effects than its predecessors.[8 44] Donati and colleagues proposed a plausible model to explain the inversed potency–onset relationship.[31] Weak compounds have more molecules to diffuse from the central compartment into the effect compartment. Once in the effect compartment, all molecules act promptly.

Chemical groups associated with specific side effects

Benzylisoquinolinium structure tends to cause histamine release, although SAR exercises have largely removed this side effect from mTc, doxacurium, cisatracurium, and the novel asymmetric isoquinolinium compounds.[10] Tropine derivatives tend to cause tachycardia.[46] It is hoped that the tachycardia in humans that may follow administration of the novel bistropinium NMB agents, if any, will be mild, equally short-acting, or even protective against the reflex bradycardia that may complicate tracheal intubation. Laudanosine may cause convulsions. The improved potency of cisatracurium reduces laudanosine production.[13 19 36]

Pro-drug or cumulation of active metabolites

A pro-drug is not a cherished idea for NMB agents. Conversion of the pro-drug to the active drug takes time and fast onset is desirable. In other words, active metabolites are not desirable. On prolonged use, cumulation of NMB effect may follow accumulation of metabolites, especially in renal failure, but, so far, metabolites of NMB agents have been weaker than their parent compounds[8 18 22 44 90 91 96] Rapacuronium is an exception. Its metabolite, 3-desacetyl rapacuronium, is more potent, slower and longer acting than rapacuronium itself.[90]

New structural features of the novel NMB agents

In the new bisquaternary isoquinolinium diester series of candidates for the 'ideal' NMB agent, the asymmetry of the chlorofumaric connecting link and the onium heads[10] is intriguing because the two receptive sites of the muscle nicotinic AchR are now known to differ.

While previous improvements on the benzylisoquinolinium compounds have succeeded in increasing the NMB potency by addition of methoxy groups, improvements in the tropinium diester series, which includes prototype G-1-64,[47] have resulted from incorporation of acyloxy groups onto the benzyl ring that quaternizes the tropinium head.[46] Acyloxylation of existing NMB relaxants, such as dTc or other isoquinolinium compounds, could make interesting future SAR exercises.

From the above, one recognizes that exceptions and outliers to the SAR rules deserve attention. For example, vecuronium qualified as an exception to the 'bisquaternary rule'. Doxacurium is an exceptional benzylisoquinolinium for not releasing histamine. Its resistance to plasma cholinesterase is an exception in the wrong direction. For its potency, rocuronium has outstanding speed of onset. Desirable outliers are often those with a wider autonomic margin of safety.[86]

Besides the classical SAR, computer-aided 'quantitative structure–activity relationship' (QSAR) has enhanced application of SAR in the development of new therapeutic agents. The traditional SAR is mainly qualitative. Its application cycle consists typically of *conception* >> *chemical synthesis* >> *pharmacological testing* >> *conception of modified compounds*. QSAR incorporates *computer-based quantitative analyses* in the cycle, often before chemical synthesis. It facilitates creation, screening, and prioritization of competing ideas 'on paper', or on the monitor. QSAR has been extensively utilized in the pharmaceutical industry, but its beneficial application in the research of NMB agents still awaits exploration and proof of viability.

CAR

While SAR relates structure to action, it is imprecise and there are numerous exceptions to the rules. Even where rules of SAR hold, and many have held and facilitated the conception of new NMB drugs, they often do not explain the mechanism of action.

As more is learned about the muscle nicotinic AchR, further progress in understanding the effect of structure on the action of NMB agents may focus on molecular conformation. Obvious conformational questions of interest include, for example, how the D-ring Ach moiety of pancuronium imparts NMB action while the A-ring Ach moiety imparts cardiovagolytic action, how methoxylation improves the NMB potency of the benzylisoquinolinium compounds, and how stereoisomerism affects potency.

Molecular shape is a fundamental concept of organic chemistry.[95] In the past, various stereomodels made of plastic or other materials have provided useful estimation of the size, shape, interatomic distance, and flexibility of molecules. Although computer chemistry is a fast growing science, the computer-aided conformational study of NMB agents is primitive at best.

Molecules prefer to exist in low energy conformations, and flexible molecules incur a smaller energy penalty to change conformation. In general, conformational flexibility means low selectivity. For practical application by non-computer chemists, user-friendly computer programs are becoming available for reliable search of low-energy molecular conformations. Besides energy minimization and conformational searches, computer modelling allows vivid visualization and accurate measurement of molecular dimensions.

Like SAR, CAR is commonly studied without considering the environment the molecule is actually in. One obvious concern is that the NMB agents may change conformation in the milieu of the body fluid and on interaction with the receptor.[5] Advanced modelling may take this into consideration in the future. Meanwhile, such caveats do not necessarily invalidate simple CAR concepts, as they have not discredited SAR rules, if cautiously interpreted. Many useful rules of SAR and CAR have been recognized in the past using plastic models.

Molecular orientation

When receptor-bound, a molecule presumably has its functional side facing the receptor and the other side exposed and facing away. Ach bound to the nicotinic receptor exposes a continuous lipophilic surface of insulating methyl groups.[5] The molecule of mTc has a convex hydrophilic side that is supposed to interact with the receptor.[93] The steroid structure of HS-342 shows crowding on the β (up) side, and Gandiha and colleagues speculated that it interacts with the receptor on the less hindered, α side.[43] Vecuronium and analogues have the D-ring Ach on the crowded β side, but their functional groups protrude out of the steroid nucleus sideward (Fig. 5). Side-specific orientation of functional groups attached to rigid NMB molecules may be important to potency.

Stereospecificity of benzylisoquinolinium NMB agents

dTc (*d*-tubocurarine) is 20 times as potent as its *l*-isomer. The benzylisoquinolinium head of cisatracurium has an R-R *cis* conformation that increases potency and reduces its side effects.[19 36] Doxacurium has three, all *trans* stereoisomers. Mivacurium has *trans–trans* (52–60%), *trans–cis* (34–40%) and *cis–cis* (4–8%) stereoisomers. The *trans–trans* and *trans–cis* isomers are favourable.[49 71] The *cis–cis* has slow elimination, but usually poses no significant risk of cumulation in clinical use because it is a minor low-potency component. The conformational commonality of the advantageous benzylisoquinolinium heads has not been well studied.

Molecular length of C10, mTc, pancuronium, gallamine and pipecuronium, and the hypothetical distance between the receptive sites of the muscle endplate AchR

If C10 can be presumed to be a straight molecule, its molecular length may hypothetically be a credible measure of the space between the receptive sites of the muscle nicotinic AchR that is available to NMB agents. Conformational studies have shown that C10 congeners indeed strongly prefer a straight conformation (personal data). Including the *vdw* radii, the lowest energy conformer of C10 measures approximately 20 Å (Fig. 10). It is interesting that low energy conformers of gallamine also prefer this molecular length (19–20 Å) (Fig. 10).[66] The middle ethonium head of gallamine is said to stabilize the two other ethonium heads.[50] This reviewer supposed that it keeps them pointed outward to span 20 Å.[68]

mTC is among the most rigid NMB agents. It measures about 18 Å in total length. Pancuronium measures 19 Å. Pipecuronium measures 21 Å, with its quaternary N atoms farthest out and least hindered among its analogues (Fig. 5). The dimension of these potent rigid NMB agents follows the ranking order of their potency, indicating that their molecules size the ‘inter-site working space’ of the receptor. These NMB agents are the most potent among their respective chemical classes. Together, they suggest 20–21 Å as an optimal dimension to fit the space actually available to NMB agents between the receptive sites of the muscle nicotinic AchR (Fig. 2).

The different interonium distances for neuromuscular and ganglion blocking potencies

The interonium distances of AH8165 (7.5 Å), pentamethonium (C5, 7.7 Å), HS-342 (8.0 Å), hexamethonium (C6, 9.0 Å), HS-310 (chandonium, 10.2 Å), protonated dTc and mTc (10.8 Å), pancuronium (11.4 Å), malouètine (12.2 Å), decamethonium (C10, 14.0 Å), and pipecuronium (16.0 Å) illustrate a trend that a short interonium distance imparts ganglion block, while a long interonium distance favours neuromuscular block.[15,75,93] Depending on the conformation of the onium head, molecular length and the interonium distance may coincide.

Among aminosteroids, pipecuronium has an interonium distance farthest away from that which is optimum for ganglion block. Correspondingly, it is among the least likely NMB agent to cause such side effects.[42,51]

Succinylcholine and C10 differ in conformation, neuromuscular block and side effects

As mentioned above, both Ach moieties of succinylcholine likely exist in a bent conformation (Fig. 4),[70] making it unlikely for one molecule of succinylcholine to span 20 Å. Furthermore, each Ach moiety of succinylcholine retains the conformation and flexibility of Ach, complete with hydrogen bond acceptor, to enable it to conform to multiple cholinergic receptors. If succinylcholine binds like Ach, with both the methonium head and the carbonyl O of one Ach moiety, its other methonium head may be prevented from pointing correctly to the other receptive site.[70] This may explain why it takes two succinylcholine molecules, as it takes two Ach molecules, to open one nicotinic Ach channel.[30,72] It also explains why succinylcholine differs from C10 in its side effects.[67]

Conformation and activity of A-ring vs *D-ring Ach moieties of aminosteroids*

The A-ring Ach moiety of pancuronium has *trans* conformation. From its centre, the charged N atom can assume a distance of 4.4 Å to the *vdw* extension of the ester O, but not a distance of 5.9 Å to the *vdw* extension of the carbonyl O. According to the rules of Beers and Reich, this A-ring Ach can be muscarinic, but not nicotinic. By contrast, the D-ring Ach moiety of pancuronium and vecuronium is *cis*. It obeys the rules of Beers and Reich to be nicotinic but not muscarinic.[69] Dacuronium (17-OH pancuronium) has an incomplete D-ring Ach moiety. Like pancuronium, however, it has an intact A-ring Ach moiety, and therefore high cardiovagal blocking potency.[1,85]

These and other concurring and contrasting examples[85] strongly suggest that while D-ring Ach is a pharmacophore for skeletal muscle nicotinic AchR, the A-ring Ach is a pharmacophore of the cardiac m_2 muscarinic receptor.[51] It explains why pancuronium and vecuronium have similar NMB potency while pancuronium alone causes a tachycardia.

Conformation of potent aminosteroid metabolites

The 3-OH metabolites of potent 3,17-diacyl aminosteroid NMB agents retain significant potency,[9,18,85,90] and 3-desacetylvecuronium is thought to cause prolonged paralysis in critically ill patients.[32,91] As discussed above, 3-OH rapacuronium is even more potent than rapacuronium itself. By contrast, the 17-OH counterparts in general are weak. This discrepancy is understandable, because the 17-acyloxy group complements the 16-onium head to complete the D-ring Ach moiety that affects neuromuscular block. It suggests that potent monoquaternary NMB agents must bind both the anionic and the hydrogen bond donor subsites of the same receptive site on the muscle nicotinic AchR.

Pipecuronium differs from other 3,17-diacyloxy aminosteroids

Pipecuronium has four functional groups, namely, 2- and 16-piperazinium heads and 3- and 17-acetoxy groups (Fig. 5). Its functional groups, however, resemble neither free Ach nor the A-ring or D-ring Ach moiety of pancuronium, and the quaternary N atoms are 3-atom distance farther away from the steroid nucleus. Without the like of the A-ring Ach moiety, pipecuronium, unlike pancuronium, does not cause tachycardia.[32,42,98] Without the like of a D-ring Ach moiety, pipecuronium probably blocks neuromuscular transmission as a bisquaternary, with two exposed and well-positioned onium heads, instead of as a monoquaternary, with a poor 16-onium,17-acyloxy pharmacophore.

Potent long-chain NMB agents

Most of these are bisquaternary, with flexible connecting chains that are 10 C-atoms long, or longer but bend without difficulty.[62,64] It is plausible to assume that they can conform to an optimal interonium distance (Fig. 2). Their stretched-out two-dimensional presentations (Fig. 6) do not meaningfully relate molecular dimensions to potency.

Conformational mechanism of the anti-muscarinic action of gallamine

Gallamine is highly cardiovagolytic.[51] The distance from the centre of N to the *vdw* extension of its ether O can readily be 4.4 Å without any energy penalty, obeying the rule of Beers and Reich for muscarinic action (Fig. 10).[68]

Conformational mechanism of neuromuscular block

The conformational features recapitulated below must be taken into consideration in explaining how NMB agents work.

1. The model nicotinic AchR arranges its pentameric subunits in a rosette. Both receptive sites must be activated for the ionic channel to open.
2. The rule of 5.9 Å of Beers and Reich for nicotinic action applies to NMB agents, as validated by the D-ring Ach moiety of pancuronium and vecuronium.

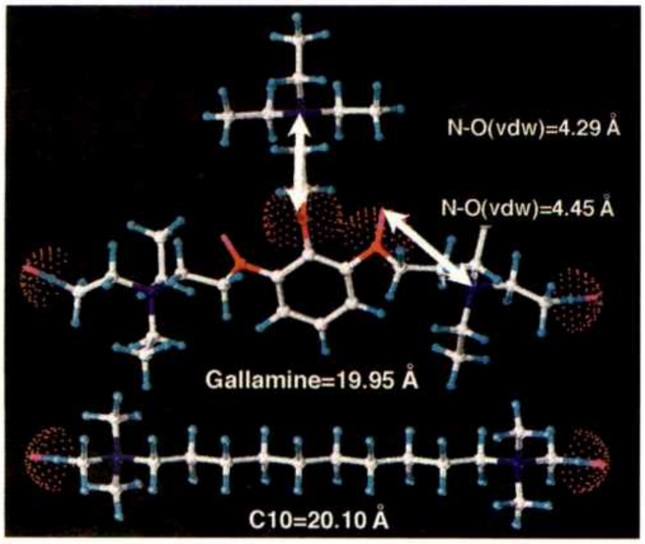


Fig 10 Molecular conformational mechanism of actions of gallamine and C10 illustrated in their low energy conformers.[68] Red atoms are O, blue atoms are N, white atoms are C and green atoms are H. Red dots around the ether O atoms and the terminal H atoms show their *vdw* radii extended in the direction marked. Total length including the *vdw* extensions is close to 20 Å for both molecules. The N-N interonium distances differ (11.30 Å, gallamine and 14.03 Å, C10). The double-arrows point to the centre of the N and the *vdw* extension of the ether O in two parts of gallamine, both of which conform to the Beers and Reich's rule of 4.4 Å for muscarinic activity.

3. C10, dTc and mTc, pancuronium and vecuronium, gallamine, and pipecuronium are among the most potent NMB agents of their respective chemical classes. Chemical diversity and variation in interonium distance notwithstanding, they all measure 18–21 Å in total length. The most potent of them, pancuronium, vecuronium, and pipecuronium measure 19–21 Å. Conformationally and pharmacologically, succinylcholine differs from other potent NMB agents. Gallamine has a third ethonium head to stabilize its molecular length.
4. Monoquaternary analogues of vecuronium depend on a properly positioned hydrogen bond acceptor that complements the active onium head for potency.
5. Bisquaternary NMB agents do not depend on hydrogen bond acceptors that complement their onium heads. Potent long-chain benzylisoquinolinium NMB agents have flexible connecting links that allow them to adopt shortened molecular lengths.
6. NMB agents lose potency if they lack a methyl quaternizing group or have the methyl group replaced by a longer alkyl or alkenyl group. Similar replacements on the 17-acyl group also reduce the potency of vecuronium analogues.
7. Pipecuronium lacks the Ach-like moiety that other aminosteroids depend on to act as potent monoquaternary NMB agents. Instead, its highly hydrophilic dimethyl onium heads protrude unhindered to permit pipecuronium to block as a potent bisquaternary.

The following conformational mechanisms of NMB action accommodate the above conditions.

- Potent NMB agents have at least two functional groups and bind two points. Potent bisquaternary agents bind the anionic subsite of both receptive sites with their onium heads, 'inter-site' (Fig. 2D and F). Potent monoquaternary agents bind the anionic subsite of one preferred receptive site and also form a hydrogen bond with the hydrogen bond donor, 'intra-site' (Fig. 2E). The D-ring Ach moiety of pancuronium and vecuronium is a NMB pharmacophore of precision and specificity.
- Alternative binding of two subsites other than in the above-specified combinations is less effective in cancelling the inter-site electrostatic attractions. Additional binding of the remaining subsites, as succinylcholine, pancuronium, and pipecuronium may do with their multiple functional groups, may slightly increase potency. However, onium heads greater in number than two (the number of anionic sub-sites) will not increase potency, except possibly by optimizing the conformation of the two binding heads.
- Depolarizing NMB agents initially bind both anionic centres while allowing depolarizing ions to flow through the channel around them (Fig. 2D). Non-depolarizing NMB agents block not only by receptive site occupation with functional groups, but also by bulk hindrance across the channel (Fig. 2E and F). Their molecules optimally measure 20–21 Å or adapt to that dimension.
- Replacing the functional methyl group with anything larger reduces NMB potency by distancing the functional groups from the receptive subsites. It also may reduce electrostatic interactions by increased lipophilicity.

This theory represents an up-dated snapshot based on the SAR and CAR rules reviewed, and is not intended to imply that receptor-relaxant interactions are static. It is open to speculations such as that long-chain NMB agents may be weakened by a rigid interonium link of non-optimal length. Like all SAR rules, species variations and exceptions must exist. How it relates to 'channel block' is beyond the scope of this review.

Conclusions

Imperfect and antiquated as they are, classical rules of SAR and their exceptions have helped the conception and development of numerous successful NMB agents. However, even with extensive SAR, refinement of any series of useful compounds still requires exhaustive trials and failure of many in multiple hopeful candidates. Like the discovery of vecuronium, any major breakthrough in NMB compound development is likely to continue to be somewhat 'accidental', because exceptional compounds are often exceptions to the rule.

The nicotinic AchR model for the skeletal muscle endplate is a pentameric macromolecule with two receptive sites, one on each α subunit where it joins its neighbouring δ or γ subunit. Two Ach molecules, one binding each receptive site, are required to open the ionic channel. Consequentially, blockage of one receptive site suffices to block neuromuscular transmission. This is the theoretical basis of action of potent monoquaternary NMB agents, which usually have two functional groups for the one receptive site.

The 'pachycurare' rule of the non-depolarizing mechanism of NMB action stands. The 'bisquaternary rule' stands, but in the case of monoquaternary aminosteroids, it is substituted by the 'two-point rule'. Potent NMB agents can block by either an 'inter-site' or 'intra-site' mechanism. The '10-carbon distance rule' applies only to the decamethylene connecting chain. Otherwise, it is the linear interonium distance and length of the molecule that determine NMB and ganglion blocking potencies, along with other factors. Onset of action, however, appears to follow no apparent rules of molecular structure or conformation, except that it is generally inversely related to potency.

Decamethonium appears to have an optimal length, 20 Å *vdw* radii included, to span the receptive sites. Potent bisquaternary non-depolarizing NMB agents of fixed molecular length measure 18–21 Å, with 20–21 Å appearing optimal. Long-chain NMB agents may have an accommodating connecting chain to adapt to the 20 Å model. Succinylcholine likely exists in short bent conformation, and takes two molecules to open one receptor ionic channel.

The 5.9 Å rule of Beers and Reich for nicotinic action can be validated for NMB agents by the D-ring Ach moiety of vecuronium and pancuronium. This Ach moiety is to date the most credible pharmacophore for the receptive site of the muscle nicotinic AchR. The 4.4 Å rule of Beers and Reich for muscarinic action can be validated by gallamine and by one O atom of the A-ring Ach moiety of pancuronium. The local steric geometry of an onium head is important to how it fits the anionic subsite of the receptor. CAR may play an increasing role in the future study of neuromuscular pharmacology, including drug design.

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SHORT COMMUNICATIONS

ADCON-L and hypotension during lumbar microdiscectomy

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ADCON-L anti-adhesion gel is used as an antifibrotic agent in surgery for herniated lumbar disc. We report seven patients undergoing lumbar microdiscectomy, in whom ADCON-L gel was applied to the nerve root before closure of the surgical site. After the administration of ADCON-L, tachycardia and hypotension were noted, and were quickly and effectively reversed by i.v. fluids and ephedrine. Since its routine introduction into our practice, we have given ADCON-L on 212 occasions, with an incidence of adverse haemodynamic reactions of 3.3%. Adverse cardiovascular reactions do not appear to have been reported before.

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ADCON-L (Gliatech, Cleveland, OH, USA) is a bioresorbable gel that provides a mechanical barrier that inhibits fibroblast migration on and around the neural structures. It consists of a polyglycan ester and absorbable pig-derived gelatin in phosphate-buffered saline. It is applied to the dura and nerve roots during surgery to prevent scar and adhesion formation. The scientific rationale for ADCON-L is based on properties of glial cells and the nature and role of the basal lamina.[1] ADCON-L is used in intraspinal lumbar surgical procedures as a temporary physical barrier to minimize post-operative peridural fibrosis, adhesions and subsequent clinical sequelae.[2] In both the USA and Europe, ADCON-L is designated a medical device and not a drug.

Methods and results

We report seven patients aged between 31 and 55 yr (four female and three male, mean age 42 yr) and ASA status 1, who received ADCON-L during first-time unilateral, single-level lumbar microdiscectomy. All patients received a standard anaesthetic consisting of induction with propofol, relaxation with vecuronium, and maintenance with nitrous oxide, oxygen and sevoflurane. Incremental doses of vecuronium were used to maintain paralysis. Patients were ventilated to maintain normocapnia and normoxia and anaesthesia was adjusted to maintain normal cardiovascular variables. Patients were placed in the knee–elbow position and a similar microsurgical procedure was performed in all cases via a para-midline approach. All procedures were uneventful and there was no evidence of dural tear. At completion of the surgical procedure, the surgical site was irrigated thoroughly and immaculate haemostasis was achieved. Before closure of the surgical site, ADCON-L gel 5 g was applied, covering all accessible surfaces of the nerve root, including the radicular foramen, between the dural sac and the posterior longitudinal ligament and between the dorsal surface of the dural sac and overlying muscle up to the level of the anterior surface of the lamina. Within seconds after the administration of ADCON-L, tachycardia and hypotension became apparent.

The mean (SEM) systolic pressure before the administration of ADCON-L was 108 (4), and after the application of ADCON-L it decreased to 80 (4). Similarly, the heart rate before ADCON-L was 65 (3) beats min^{-1} and after ADCON-L it increased to 94 (7) beats min^{-1} (Fig. 1). Hypotension was restored to the pre-induction level within an average of 8.7 min (range 3–15 min) after the administration of i.v. fluids (Hartman's solution, mean volume 1000 ml, and Gelofusine, mean volume 500 ml) and ephedrine 12–15 mg given incrementally. None of these hypotensive episodes was associated with hypoxaemia and the ECG showed sinus tachycardia throughout. No patient

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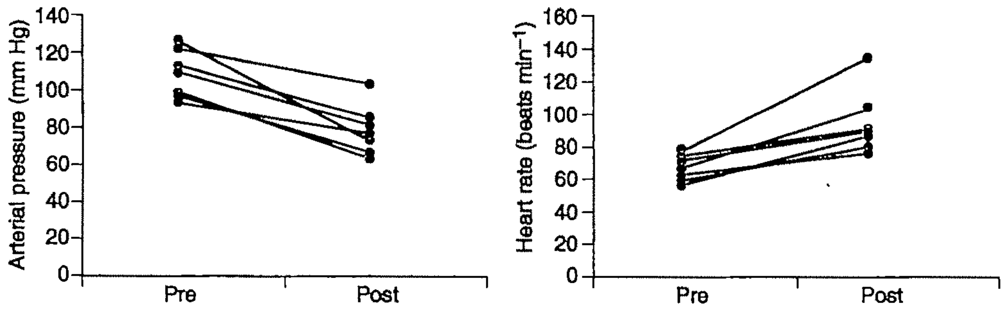

Fig 1 Changes in arterial pressure and heart rate in seven patients undergoing lumbar microdiscectomy, before (Pre) and after (Post) administration of ADCON-L.

developed bronchospasm, urticaria or erythema and there was no increase in body temperature. After cardiovascular stability had been restored, a blood sample was obtained and serum tryptase (an indicator of mast cell degranulation and therefore histamine release) was measured.[3] Serum tryptase was not identified in any of the patients. All patients remained stable post-operatively and were discharged the next day after an uneventful recovery.

Discussion

Since its routine introduction into our practice, we have given ADCON-L on 212 occasions and it has led to adverse haemodynamic effects in seven cases. No side-effects have been noted in the last 100 consecutive cases.

Mechanisms that may account for ADCON-L-induced cardiovascular instability include anaphylactic reaction, direct myocardial depression and systemic vasodilatation. Anaphylactic reaction is unlikely because other systemic manifestations of allergy, such as erythema, urticaria, salivation, cyanosis or bronchospasm, were absent. In addition, serum tryptase was not identified in any of the cases.

Myocardial depression and systemic vasodilatation may have occurred secondarily to the systemic absorption of ADCON-L, although, because this substance is used as an implant and not as a drug, it has not been investigated to determine if it has vasoactive properties. However, i.v. fluids and vasopressors were required in moderate doses in order to treat the haemodynamic changes. Intravenous fluids improve myocardial contractility by improving cardiac preload, and they also reverse the haemodynamic effects of a vasodilated circulation. Ephedrine has chronotropic, inotropic and vasoconstrictor properties and therefore directly improves myocardial contractility and reverses systemic vasodilation. Heart rate decreased and blood pressure increased after the administration of i.v. fluid and ephedrine, and we propose that the mechanism of the observed haemodynamic changes is myocardial depression and systemic vasodilatation. The reactions are similar to those described after the use of methylmethacrylate cement, which is used to fix orthopaedic prostheses. In these instances, a transient fall in blood pressure within 1 or 2 min of inserting the methylmethacrylate cement into the medullary canal of the femur is often observed. Usually, arterial pressure returns to normal in 3–5 min. The adverse effects of methylmethacrylate include systemic vasodilatation and direct myocardial depression secondary to absorption of the methylmethacrylate cement.[4–6] Embolism of fat, air or bone marrow can occur when methylmethacrylate cement is used, but there is no reason to believe that these may have occurred after the administration of ADCON-L.

There are important implications for the anaesthetist whenever ADCON-L is used. We now routinely administer Hartman's solution 1000 ml and Gelofusine 500 ml during surgery and before ADCON-L is administered. In more than 100 consecutive microdiscectomies, no episodes of hypotension have been observed since this practice was introduced.

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Randomized controlled study of colloid preload before spinal anaesthesia for Caesarean section[†]

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We randomized women having elective Caesarean section to receive either no preload (control group, n=33) or 4% gelatin solution (Gelofusine) 15 ml kg^{-1} (colloid group, n=35) i.v. before spinal anaesthesia. Intravenous metaraminol was titrated at 0.25–0.75 mg min^{-1} to maintain systolic arterial pressure (SAP) in the target range 90–100% of baseline after the spinal injection. The control group required more vasopressor in the first 10 min [median 1.7 (range 0–2.9) mg *vs* 1.4 (0–2.8), P=0.02] at a greater maximum infusion rate [0.5 (0–0.75) *vs* 0.25 (0–0.5) mg min^{-1}, P=0.0005] and had a lower minimum SAP [90 (51–109) *vs* 101 (75–127) mm Hg, P=0.006] than the colloid group. Nausea was less frequent in the colloid group (6 *vs* 24%) but neonatal outcome was similar in the two groups. Colloid preload improved haemodynamic stability but did not affect neonatal outcome when arterial pressure was maintained with an infusion of metaraminol during spinal anaesthesia for Caesarean section.

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The use of intravenous fluid preload before spinal anaesthesia for Caesarean section is controversial. Crystalloid preload has minimal effect on the incidence of hypotension, vasopressor requirement and maternal and neonatal outcome.[1 2] Fewer data are available on colloid preload, which has not been compared previously with a control of no preload. Because colloid solutions augment circulating volume more than crystalloids, they may be more effective in maintaining arterial pressure.[3] The aim of this study was to evaluate preloading with gelatin solution 15 ml kg^{-1} *vs* no preload in patients in whom we maintained arterial pressure with an infusion of metaraminol. We chose to investigate gelatin solutions because they are the most commonly used colloid in our institution and because they have a relatively short intravascular half-life that is well matched to the usual duration of surgery for Caesarean delivery.

Methods and results

After ethics committee approval and written informed consent, we recruited 70 ASA I–II women with term singleton pregnancies having spinal anaesthesia for elective Caesarean section. Patients with hypertension, pre-eclampsia, cardiovascular or cerebrovascular disease, known fetal abnormality or any contraindication to spinal anaesthesia were excluded. Ranitidine and sodium citrate were given for premedication. After arrival at the operating theatre, baseline systolic arterial pressure (SAP) and heart rate (HR) were calculated as the mean of three successive measurements with a difference of no more than 10%, taken at intervals of 1 min.

We allocated patients randomly using sequentially numbered, coded envelopes, to receive no preload (control group) or 4% succinylated gelatin solution 15 ml kg^{-1} (Gelofusine; B. Braun Medical, St Gallen, Switzerland) i.v. over 15 min (colloid group). This volume is at the upper end of the range of volumes investigated previously.[3] Preloading was supervised by a research nurse. To maintain blinding, the anaesthetists and other investigators remained outside the operating theatre during the preloading period. Patients were not blinded.

Immediately after the preloading period, spinal anaesthesia was induced with the patients in the lateral position, using 0.5% bupivacaine 2.0 ml plus fentanyl 15 µg. Patients were then turned supine with left lateral tilt and lactated Ringer's solution was infused at 2 ml min^{-1}, controlled with

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an infusion pump. Arterial pressure was measured at 1-min intervals beginning 1 min after the spinal injection. An i.v. infusion of metaraminol 0.5 mg ml^{-1} was started after the SAP had decreased to <90% of baseline. A bolus of metaraminol 0.5 mg was given and the infusion was titrated at 0.25–0.75 mg min^{-1} with a syringe pump to maintain SAP in the target range 90–100% of baseline, using a protocol we have described previously.[2 4] We recorded the rate of metaraminol infusion each minute and the cumulative consumption of metaraminol 5 and 10 min after spinal injection and at the time of uterine incision.

Ten minutes after spinal injection, the block level was checked and preparation for surgery was started. Oxygen 5 litre min^{-1} was given by face mask until delivery. Times of skin incision, uterine incision and delivery were recorded with a stopwatch. Nausea and vomiting not associated with hypotension were treated with metoclopramide 10 mg i.v. After delivery, oxytocin 10 IU was given i.v. and the study was terminated. Apgar scores were assessed at 1 and 5 min by the attending paediatrician and arterial and venous blood samples were taken from a double-clamped segment of umbilical cord for immediate blood gas analysis.

Prospective power analysis based on data from previous studies in our department showed that 33 patients per group would give 80% power with $\alpha=0.05$ to detect a 20% difference between groups in the total amount of metaraminol required. To allow for potential dropouts, we recruited 35 patients per group. Data are presented as median (range) and were analysed using Mann–Whitney and Fisher's exact tests. Serial haemodynamic measurements up to the time of the earliest uterine incision were analysed by repeated measures analysis of variance.[5] $P<0.05$ was considered significant.

Two patients in the control group were excluded because of protocol violations. Except for one patient in the colloid group, all patients received metaraminol. Patient characteristics, block height and surgical times were similar between groups.

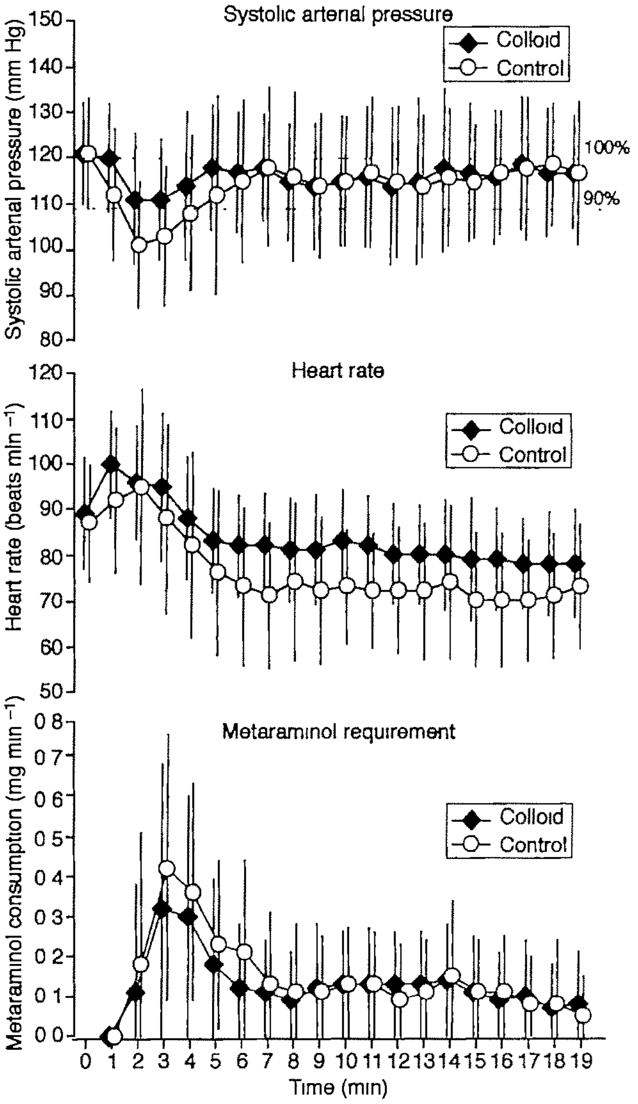

Fig 1 Changes in systolic arterial pressure (SAP), heart rate and metaraminol consumption against time. Values are mean (SD) Dotted lines show approximate target range for SAP. Serial changes in SAP were similar in the two groups, although the pattern of change was different between groups ($P=0.03$) Serial changes in heart rate were significantly different between groups ($P=0.01$) Serial changes in metaraminol consumption were similar in the two groups

Haemodynamic changes and metaraminol infusion rates are shown in Fig. 1. There was a significant change in SAP over time ($P<0.0001$); this did not differ between groups ($P=0.26$), although the pattern of change was different between groups (significant group × time interaction, $P=0.03$). The minimum recorded SAP was lower in the control group than in the colloid group [90 (51–109) *vs* 101 (75–127) mmHg, 95% confidence interval (CI) of the difference 3–16 mmHg, $P=0.006$]. Twenty-one patients (64%) in the control group had a decrease in SAP of greater than 20% compared with 11 patients (31%) in the colloid group ($P=0.01$). Heart rate was lower in the control group than in the colloid group ($P=0.01$), with no significant group × time interaction ($P=0.8$). Serial changes in metaraminol consumption were similar in the two groups; however, compared with the colloid group, the control group had a greater cumulative metaraminol consumption at 5 min [1.1 (0–1.9) mg *vs* 0.8 (0–1.8) mg; 95% CI of the difference 0–0.4 mg, $P=0.01$] and 10 min [1.7 (0–2.9) *vs* 1.4 (0–2.8) mg; 95% CI of the difference 0–1.7 mg, $P=0.02$] and required a greater maximum infusion rate [0.5 (0.25–0.75) *vs* 0.25 (0–0.5) mg min^{-1}; 95% CI of the difference 0–0.25 mg min^{-1}, $P=0.0005$]. The total dose of metaraminol at uterine incision was similar between groups [3.1 (0–4.8) *vs* 3.5 (0.9–6.3) mg; 95% CI of the difference –0.1 to 1.1 mg, $P=0.08$].

Eight patients (24%) in the control group had nausea or vomiting *vs* two patients (6%) in the colloid group ($P=0.04$) Apgar scores were similar between groups, with all scores $\geqslant 7$. Umbilical arterial pH was similar in the control group [median 7.31 (range 7.23–7.39)] and the colloid group [7.30

(7.20–7.38)]. No problems related to the anaesthetic were identified at routine follow-up the day after surgery.

Comment

Our study showed that preload with gelatin solution 15 ml kg^{-1} improved haemodynamic stability during spinal anaesthesia for Caesarean section when arterial pressure was maintained with a metaraminol infusion. This was evident in the lower maximum infusion rate and the smaller early vasopressor consumption required to maintain arterial pressure in the target range and the smaller maximum reduction in SAP in the colloid group compared with the control group. Furthermore, colloid preload reduced the incidence of nausea and vomiting. Therefore, preload with a colloid may be advantageous in patients in whom large fluctuations in arterial pressure and heart rate and large doses of vasopressors need to be avoided.

However, preload with colloids has potential disadvantages, including cost and the risks of haemodilution, fluid overload and anaphylactoid reactions.[6] Therefore, in healthy patients, some clinicians may prefer to rely on vasopressors alone and not to use colloids routinely. This approach appears safe because we found neonatal outcome in the control group was as good as in the colloid group. However, the increased early vasopressor requirement in non-preloaded patients should be noted.

Our findings are similar to those of a previous study in which we investigated preload with 20 ml kg^{-1} of crystalloid using a similar method.[2] In both of these studies, we chose to maintain arterial pressure with an infusion of metaraminol. Although ephedrine has been recommended more commonly as a vasopressor in obstetrics, we have shown previously that an infusion of metaraminol results in less fetal acidosis than an infusion of ephedrine.[4]

Some patients in our study had isolated and transient low arterial pressures recorded. This was not associated with adverse neonatal outcomes and might have been avoided by starting the vasopressor infusion earlier rather than waiting for the initial decrease in arterial pressure, as specified in our protocol.

In summary, we found that when maternal arterial pressure was maintained with an infusion of metaraminol, colloid preload improved haemodynamic stability and reduced maternal nausea and vomiting but had no effect on neonatal outcome.

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Subclinical hepatic dysfunction in laparoscopic cholecystectomy and laparoscopic colectomy

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Laparoscopic surgery causes a reduction in hepatic blood flow due to a number of factors, including raised intra-abdominal pressure, the neurohumoral response to surgical

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stress and the effect of patient position. The clinical significance of the phenomenon is not fully understood. Plasma concentrations of alcohol dehydrogenase (AD) and glutathione S-transferase (GST), which are concentrated in the centrilobular acinus of the liver, sensitively reflect hepatic hypoperfusion, and can be used to monitor reductions in hepatic blood flow. We compared perioperative AD, GST, aspartate aminotransferase (AST, normal range 14–32 IU litre^{-1}) and alanine aminotransferase (ALT, normal range 8–41 U litre^{-1}) concentrations in patients undergoing laparoscopic cholecystectomy or laparoscopic colectomy to study how patient position and surgical manipulation of the liver affect hepatocellular integrity during laparoscopy. There were significant postoperative increases in AD and GST in the cholecystectomy group [mean (SD) peak concentration 10.8 (4.7) U litre^{-1} and 113 (55) µg litre^{-1} respectively]. Although the duration of pneumoperitoneum was longer in the colectomy group, there were no comparable perioperative increases in AD and GST in this group [peak concentration 4.0 (4.0) U litre^{-1} and 33 (35) µg litre^{-1} respectively]. AST and ALT on the first postoperative day were significantly higher in the laparoscopic cholecystectomy group (41 and 34 U litre^{-1} respectively) than in the laparoscopic colectomy group (24 and 18 U litre^{-1}; $P<0.05$ for each). These results indicate that patient position and the effects of surgical manipulation of the liver affect perioperative hepatic perfusion significantly.

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Keywords: enzymes, alcohol dehydrogenase; enzymes, glutathione S-transferase; surgery, laparoscopy; surgery, cholecystectomy; surgery, colectomy

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Laparoscopic cholecystectomy using carbon dioxide insufflation induces intraoperative cardiovascular changes. These are due to a number of factors, including the reverse Trendelenburg position; increased intra-abdominal pressure; the neurohumoral response to surgical stress; and the effects of carbon dioxide absorption.[1] A previous study has shown that laparoscopic cholecystectomy cause transient hepatic hypoperfusion.[2] However, the clinical significance of this change remains unclear and detailed studies are warranted.[3]

Hepatic alcohol dehydrogenase (AD)[4] and glutathione S-transferase (GST)[5] are concentrated in centrilobular hepatocytes and are sensitive enzymes of hepatocellular damage. Thus, perioperative AD and GST levels should clarify the clinical significance of the reduced hepatic blood flow associated with laparoscopic procedures. Changes in splanchnic blood flow have also been linked to the effects of patient position in laparoscopic surgery.[6] A comparison of laparoscopic cholecystectomy and laparoscopic colectomy, which are performed using different patient positions and at different surgical sites, may reveal the effects of positioning and surgical manipulation on hepatic perfusion.

In this study we compared perioperative plasma concentrations of AD and GST in these two groups of patients to evaluate the effects of laparoscopic surgery on hepatocellular integrity. Perioperative changes in serum transaminase concentrations were also monitored.

Methods and results

With approval from the institutional Ethics Committee and informed consent, 14 patients undergoing either laparoscopic cholecystectomy (n=7) or laparoscopic colectomy (n=7) were studied. All patients were premedicated with oral diazepam 5 mg and i.m. atropine 0.5 mg. Anaesthesia was induced with thiopental 4–5 mg kg^{-1} and vecuronium 0.1 mg kg^{-1}, and was maintained using sevoflurane 2–3%, nitrous oxide 66% and oxygen, with intermittent fentanyl and vecuronium. Patients were ventilated mechanically, and Pa_{CO_2} was maintained between 4.0 and 4.7 kPa.

Carbon dioxide insufflation was performed to facilitate laparoscopy, and intra-abdominal pressure was maintained between 1.1 and 1.6 kPa. Patients in the laparoscopic cholecystectomy group were positioned in the reverse Trendelenburg position, while those in the laparoscopic colectomy group were positioned in the Trendelenburg position. Arterial blood was sampled after the induction of anaesthesia, at the end of surgery and 1, 3 and 6 h after surgery for the estimation of plasma AD, GST, aspartate aminotransferase (AST, normal range 14–32 U litre^{-1}) and alanine aminotransferase (ALT, normal range 8–41 U litre^{-1}) concentrations.

Plasma AD concentrations were measured using the method described by Kato and colleagues.[7] GST concentrations were measured using the Hepkit enzyme immunoassay (Biotrin, Dublin, Irish Republic). AST and ALT

Table 1 Perioperative plasma AD, GST and transaminase concentrations in patients undergoing laparoscopic cholecystectomy (Chole) and laparoscopic colectomy (Colon) (*n*=7 for each group) Data are expressed as mean (SD). n/a = not available. $^{*}P<0\ 05$ *vs* laparoscopic colectomy, $^{\dagger}P<0\ 05$ *vs* after induction in each subgroup

Enzyme	Type of surgery	After induction	End of surgery	After surgery			
				1 h	3 h	6 h	1 day
AD	Chole	0 8 (0.6)	9.7 (4 0)*†	10.8 (4.7)*†	7 2 (3.0)†	4 3 (2.4)	n/a
(U litre^{-1})	Colon	1.4 (1.1)	4.0 (4 0)	3 9 (3.9)	2 7 (2.5)	1 7 (1 2)	n/a
GST	Chole	5 (3)	113 (55)*†	58 (38)*†	17 (5)	16 (6)	n/a
(μg litre^{-1})	Colon	8 (6)	33 (35)	18 (21)	16 (20)	12 (10)	n/a
AST	Chole	16 (2)	25 (7)	32 (9)	36 (12)	38 (12)*	41 (14)*†
(U litre^{-1})	Colon	21 (7)	23 (8)	24 (10)	25 (10)	21 (10)	24 (6)
ALT	Chole	9 (4)	14 (4)*	16 (4)*	17 (5)*	19 (6)*	34 (10)*†
(U litre^{-1})	Colon	9 (3)	10 (3)	11 (4)	11 (4)	11 (4)	18 (5)†

concentrations were measured with a Hitachi 7600 automatic analyser (Hitachi, Tokyo, Japan).

Data are expressed as mean (SD). Statistical analysis was performed using the unpaired *t*-test and analysis of variance. $P<0.05$ was considered clinically significant.

There were no significant differences in sex, age [59 (10) *vs* 67 (8) yr), weight [58 (13) *vs* 57 (14) kg] or height [158 (8) *vs* 162 (11) cm] between the laparoscopic cholecystectomy and laparoscopic colectomy groups. The durations of surgery and pneumoperitoneum were shorter in the laparoscopic cholecystectomy group than in the laparoscopic colectomy group [surgery, 62 (32) *vs* 225 (66) min; pneumoperitoneum, 39 (20) *vs* 125 (59) min]. The total dose of fentanyl in the two groups was 57 (79) and 100 (58) µg respectively and that of vecuronium 7.7 (1.9) and 14.8 (4.9) mg.

The AD concentration in the laparoscopic cholecystectomy group was significantly elevated by the end of surgery and remained significantly elevated for 3 h after surgery (Table 1). There were no significant increases in AD in the laparoscopic colectomy group. AD concentrations at the end of the procedure and 1 h after surgery were higher in the laparoscopic cholecystectomy group than in the laparoscopic colectomy group.

The GST concentration in the laparoscopic cholecystectomy group was significantly elevated at the end of the procedure and 1 h after surgery, but decreased rapidly and had returned almost to the preoperative value 3 h after surgery. As with AD, there were no significant postoperative increases in GST concentration in the laparoscopic colectomy group. The GST concentration in the laparoscopic cholecystectomy group was higher at the end of the procedure and 1 h after surgery than in the laparoscopic colectomy group. The AST concentration in the laparoscopic cholecystectomy group was significantly elevated on the first day after surgery. The mean value was significantly higher in the laparoscopic cholecystectomy group than in the laparoscopic colectomy group 6 h after surgery and on the first day after surgery. The ALT concentration was significantly elevated on the first day after surgery in both groups. It was higher in the laparoscopic cholecystectomy group than in the laparoscopic colectomy group at all time-points.

Comment

We observed transient perioperative increases in AD and GST in the patients undergoing laparoscopic cholecystectomy, but no such increases were observed in the laparoscopic colectomy group. In both groups, AD and GST returned rapidly to near-preoperative concentrations after surgery, and none of the patients presented with clinical hepatic dysfunction after surgery.

Hepatic hypoperfusion during laparoscopic cholecystectomy has been reported previously.[2 3] This finding was attributed to the combined effects of elevated intra-abdominal pressure, hypercapnia and the position of the patient. Humoral factors, such as vasopressin released from the pituitary, may also be involved in changes in hepatic blood flow during laparoscopic surgery.[8] Comparison of laparoscopic cholecystectomy and colectomy by the use of a sensitive marker of hepatic dysfunction, such as AD and GST,[5] may clarify which factors account for this change, as these two procedures involve different patient positions and types of surgical manipulation.

Although the normal ranges of AD and GST concentrations have not been clearly defined, the preoperative upper concentration limits of these enzymes have been reported as 5 U litre^{-1} and 10 µg litre^{-1} respectively. The increases in AD and GST observed in this study indicate that laparoscopic procedures are associated with disturbances in hepatocyte integrity. As much smaller fluctuations in GST were observed during mastectomy under sevoflurane anaesthesia,[9] these changes can be attributed to the laparoscopic procedure. Patients in the laparoscopic cholecystectomy group showed significantly greater postoperative increases in plasma AD and GST than those in the laparoscopic colectomy group. Although the duration of pneumoperitoneum was longer in patients undergoing laparoscopic colectomy than in the laparoscopic cholecystectomy group, perioperative AD and GST concentrations were not correlated with the duration of pneumoperitoneum in either group. Despite the small sample size, these findings support the theory that factors other than elevated intra-abdominal pressure have a significant effect on hepatic perfusion during laparoscopic surgery.

One possible factor is the effect of patient position on blood flow. Sato and colleagues used transoesophageal echocardiography to monitor hepatic blood flow during laparoscopic cholecystectomy and concluded that the combination of pneumoperitoneum and head-up positioning resulted in decreased hepatic perfusion.[3] Junghans and colleagues also found that the combination of the head-up position with a higher intra-abdominal pressure resulted in the greatest disturbance in hepatic perfusion.[10]

The effects of surgical manipulation of the liver and the neurohumorally mediated response to surgical stress may also contribute to the transient disturbance of hepatocyte integrity. As direct compression of the liver is not severe in laparoscopic cholecystectomy, it is probable that neurochemical factors such as vasopressin and norepinephrine play a more significant role in causing the transient reduction in hepatic blood flow. Additionally, application of diathermy to the liver surface might contribute to the elevated AD, GST and transaminase concentrations after laparoscopic cholecystectomy. However, the effect of diathermy should be immediate and zone-independent, and AD, GST and the transaminases should therefore increase simultaneously. As this was not the case, we believe that the observed change was caused by a disturbance of intraoperative hepatic perfusion.

Our findings show that the changes in the plasma concentrations of these enzymes follow somewhat different time-courses. We assume that the changes in AD and GST reflect an identical reduction in hepatic blood flow, and that the differences in the time-courses are attributable to the different plasma half-lives of the two enzymes. It has not yet been determined whether AD or GST provides the more accurate indicator of hepatic hypoperfusion.

In conclusion, we found that patients undergoing laparoscopic cholecystectomy showed signs of subclinical hepatocellular injury attributable to hepatic hypoperfusion. The finding that there were significantly higher perioperative increases in plasma AD and GST in patients undergoing laparoscopic cholecystectomy than those undergoing laparoscopic colectomy suggests that the increased intra-abdominal pressure caused by carbon dioxide insufflation was not the sole cause of the hepatocellular injury. The head-up positioning of the patient, the effects of direct manipulation of the liver and the neurohumoral response to upper abdominal surgical stress may all play important roles in the disturbance of hepatic perfusion during laparoscopic cholecystectomy. Further study of these individual factors is warranted.

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Effects of the auditory stimuli of an auditory evoked potential system on levels of consciousness, and on the bispectral index†

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Investigators in the field of depth of anaesthesia monitoring sometimes measure the auditory evoked potential (AEP) and the Bispectral Index (BIS) concurrently. However, the auditory stimuli required to generate an AEP may increase the level of consciousness, and cause an increase in the BIS. They may also alter the BIS by producing phase-locked harmonics in the surface electroencephalogram. The aim of this study was to determine if AEP stimuli have clinically significant effects on levels of consciousness and BIS values during sedation and general anaesthesia. Ten healthy adult patients were studied by measuring and recording the BIS for 6 epochs of 5 min each. The first 3 epochs took place during steady-state sedation, during which time the Observer's Assessment of Awareness/Sedation (OAA/S) score was also measured. The second 3 epochs took place during steady-state anaesthesia. During alternate epochs, patients were subjected to the auditory stimuli generated by an AEP system. The auditory stimuli were not associated with a change in BIS values (during sedation and anaesthesia) or OAA/S scores (sedation).

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Keywords: measurement techniques, auditory evoked potential; monitoring, bispectral index; sedation; anaesthesia, general

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At present there is no 'gold standard' measure of anaesthetic depth. The traditional clinical signs are surrogate measures, which assess autonomic activity and are unreliable predictors of conscious perception and recall.[1 2] Newer measures derived from analyses of the electrocardiogram (respiratory sinus arrhythmia) and the electroencephalogram (EEG) (Bispectral Index (BIS), auditory evoked potential (AEP) and approximate entropy) are undergoing further evaluation. These studies sometimes involve comparisons of clinical signs with simultaneous measurements of combinations of the newer variables.[3–6]

Repetitive auditory stimuli are required to generate an AEP. Theoretically, these may alter the BIS by causing sufficient stimulation to increase the level of consciousness. In addition they may cause an indirect effect on the BIS. Bispectral analysis assesses phase relationships among component frequencies in the EEG. By introducing phase-locked harmonics, the repetitive stimuli may cause false alterations in the BIS. We, therefore, evaluated the effect of the AEP clicks on levels of consciousness and BIS values during steady-state sedation and anaesthesia.

Methods and results

After ethics committee approval and informed consent, 10 adult patients, ASA status I–III, presenting for elective plastic or lower limb orthopaedic surgery were studied. Exclusion criteria included a history of deafness, obesity, hiatus hernia, or psychiatric disorders.

A custom-made AEP system was used to generate clicks at a frequency of 6.9 Hz and volume of 70 dB. An A-2000 BIS monitor (Software v3.3, Aspect Medical Systems, Newtown, USA) was used to generate BIS data, which were recorded electronically every 5 s. These data were recorded for 30 min, comprising 6 epochs of 5 min, during which the AEP clicks were alternately switched on or off. Patients 1, 3, 5, 7, and 9 had the clicks on during odd-numbered epochs,

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†Preliminary results presented at ESA, Gothenburg, April 2001.

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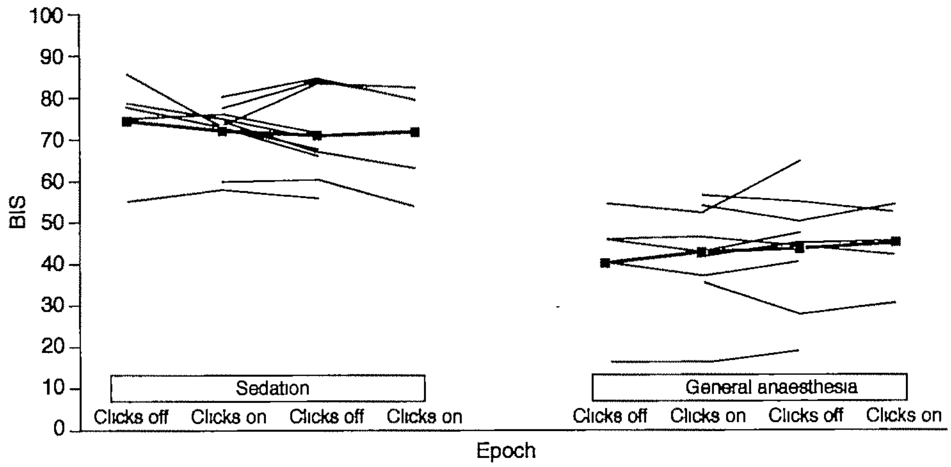

Fig 1. Mean BIS values for individual patients during 3rd minute of each epoch. Heavy line represents the mean.

and off during even-numbered epochs, while the reverse applied to the remaining patients. The first three epochs were recorded while patients were sedated before induction of anaesthesia, and the remaining three after induction of anaesthesia. Heart rate, non-invasive arterial pressure, and oxygen saturation were recorded every 5 min.

No sedative pre-medication was given. On arrival in the pre-anaesthetic care unit, routine monitoring was instituted and baseline measurements recorded. An i.v. cannula was inserted into the dorsum of the non-dominant hand and a target-controlled infusion (TCI) of propofol was started at an initial target blood concentration of 1 $\mu g\ ml^{-1}$ using a Diprifusor (AstraZeneca, UK). The three patients undergoing lower limb orthopaedic surgery first had a lumbar epidural catheter inserted. Bupivacaine 0.5%, 10 ml, was injected into the epidural space, and the patient was observed for 20 min before the propofol TCI was started. During this period, 500 ml of modified gelatin solution (Geloflex, Braun Medical, UK) was administered. There were no episodes of hypotension (prospectively defined as systolic arterial pressure <80 mm Hg, or a decrease of >30% from baseline).

During the period of sedation, a single investigator performed the Observer's Assessment of Awareness/Sedation (OAA/S) every minute. The target propofol concentration was gradually increased until the OAA/S score was 4 (response to name spoken in normal tone), and the patient was lying peacefully, with closed eyes. The target blood concentration was then set to the current estimated effect-site concentration. Once the estimated blood and effect-site concentrations had equilibrated, the first 15 min of BIS recording was started. The amount of background noise was kept to a minimum, and the patient was not disturbed except to assess sedation and measure arterial pressure.

At the end of the first 15 min, the propofol TCI was continued at the same target concentration, and the patient was moved into the operating theatre. After he or she had breathed 100% oxygen for 3 min, anaesthesia was induced and maintained using TCI propofol, supplemented with TCI remifentanil or alfentanil in patients undergoing plastic surgery. A laryngeal mask airway (LMA‡) was inserted and the patients' lungs were mechanically ventilated using 40% oxygen in air, except for the orthopaedic patients who breathed the same mixture spontaneously. The target propofol concentration was reduced to a level just above the estimated effect-site concentration required for loss of consciousness and LMA insertion. After equilibration, the target concentrations of propofol and opioid were kept constant, and the second 15 min period of BIS recording began. The study terminated at the end of this period, and the surgeon was allowed to start the operation.

OAA/S scores are presented as median (range), and all other data as mean (SD). For individual patients median OAA/S scores and mean BIS values were derived by combining epochs during which the clicks were, respectively, on and off. All five OAA/S scores for each epoch were included, whereas only the middle (third) minute of BIS data from each epoch was used, to ensure that only BIS values derived from EEG data recorded during the current epoch were included. Within-subject analysis (two-way ANOVA) was used to assess the effect of the clicks on the BIS. OAA/S scores were compared using the Wilcoxon rank-sum test. *P*<0.05 was regarded as statistically significant.

Five males and five females were studied. Mean age, weight, and height were 39.8 (20.3) [range 17–69] yr, 68.3 (17.1) kg, and 168 (13.3) cm. The effect-site propofol concentrations required for sedation and maintenance of anaesthesia were 1.6 (0.4) and 3.6 (1.0) $\mu g\ ml^{-1}$, respectively. During sedation, the median OAA/S scores were 4 (3–4) with the clicks on, and 4 (3–5) with the clicks off

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(P>0.37). There was no difference between OAA/S scores in the first minute after starting the clicks compared with subsequent minutes. During general anaesthesia, stopping or starting of the clicks was not associated with a change in clinical signs of depth of anaesthesia, except in one patient who made some spontaneous movements during epoch 6, soon after the clicks were switched off. These movements stopped without any intervention.

Mean BIS values for individual patients are shown in Figure 1. BIS data were not collected for one patient during epoch 6, as the study was terminated when the surgeon insisted on starting the operation. During sedation, the mean (SD) BIS values were 75.2 (9.8) when the clicks were on and 74.9 (9.8) when the clicks were off. For general anaesthesia the corresponding figures were 46.0 (13.6) and 47.7 (16.2), respectively. ANOVA showed a large between-subject variation but no significant within-subject variability in the BIS associated with the clicks (P=0.34 for sedation and P=0.95 for anaesthesia). The mean within-subject difference in the BIS (value with clicks on less value with clicks off) was –0.96 (95% CI: –3.13 to 1.2) for sedation, and –0.17 (95% CI: –6.3 to 6.0) for general anaesthesia.

Comment

In this study, AEP clicks did not alter the clinical signs of depth of sedation or anaesthesia, and were not associated with a change in the BIS.

There are various reasons why the AEP clicks may not have an effect on the BIS. The first is that even if the AEP clicks are initially rather loud, the stapedius reflex quickly causes accommodation. This reflex attenuates the amplitude of the electrical impulses passing along the auditory pathways. The second is that the amplitude of the AEP arriving at the cortex of the brain is many orders of magnitude smaller than the background EEG. This is why signal averaging techniques are necessary to extract the AEP waveform from the EEG. The A-2000 monitor utilizes a combination of time domain, frequency domain, and bispectral analyses, none of which is likely to be sensitive to very small amplitude signals.

It is possible that our result is falsely negative. With 10 subjects, and an α level of 0.05, our study can only accept the null hypothesis with power >80% for a mean within-subject difference in BIS of 2.7 during sedation and 7.7 during anaesthesia (the SD of the within-patient differences in the current study were 3.0 and 8.6, respectively). To exclude a smaller difference between groups with adequate power, a far greater sample size is necessary.

In conclusion, based on the patients we have studied we have not found evidence that the AEP clicks cause an alteration in the level of consciousness or the BIS.

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Long-term consequences of repeated pentobarbital anaesthesia on choice reaction time performance in ageing rats

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Recent studies have suggested that anaesthesia may be a factor in cognitive decline with age. We examined the effect of repeated (eight times) anaesthesia with pentobarbital on reaction time performance in rats in a longitudinal study. Treated rats had faster response times and made more premature responses than the control rats when they were older than 21 months. The results suggest that repeated anaesthesia during the lifespan can lead to an increase in impulsivity, as assessed by a choice reaction time test, during the later stages of life in the rat. These findings support the theory that repeated anaesthesia is a biological factor that affects cognitive ageing.

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Keywords: age factors; risk; cognition

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Several studies have shown that patients who undergo anaesthesia and surgery may develop a cognitive deficit in the postoperative period and that age is a major risk factor. These impairments seem to be short-lasting and generally disappear after several days to weeks,[1–3] although two large-scale studies have shown that 5–10% of elderly patients show a cognitive deficit that persists for several months[4 5] and may be permanent.[6]

The many, uncontrollable variables in human subjects make appropriate studies difficult and an animal model would be helpful. We describe a longitudinal experiment in which the effects of repeated anaesthesia on reaction time were examined in rats. We repeatedly anaesthetized and tested their cognitive performance with a choice reaction time (CRT) task throughout life. The study continued until the rats were 26 months old, when rats may be considered 'aged'. If anaesthesia is a vulnerability factor for cognitive ageing, the performance of the experimental groups should diverge in the course of their lifespan.

Methods and results

Animals

All experimental procedures were approved by the research ethics committee of Maastricht University for animal experiments and met government guidelines. Twenty-seven Lewis rats were obtained from the animal facilities of Maastricht University. The animals were housed individually in standard Makrolon cages on sawdust bedding in an air-conditioned room (about 20°C) under a 12/12-h reversed light/dark cycle (lights on from 18.00 to 6.00 h) and had free access to food and water.

Experimental design

At the age of 6–8 months, the rats were trained on the CRT task[7] after food deprivation to 85% of free feeding weight, matched for their reaction time performance and assigned to the control (n=12) or treatment (n=15) group. Rats in the treatment group were then anaesthetized and the CRT was repeated 2 days later. Free feeding was then permitted until the next test session. The control group was treated and tested identically apart from the anaesthesia. Thereafter, the sequence of food deprivation, training, CRT, anaesthesia and CRT was repeated at intervals of 2.5 months, when the rats were 6, 8.5, 11, 13.5, 16, 18.5, 21 and 23.5 months old. Two months after the last study period the CRT was repeated for the last time, as the number of rats that responded reliably in the behavioural task was reduced to eight and nine in the control and treatment groups respectively. After the final behavioural test, when the rats were 26 months old, the animals were killed and the brain was removed for biochemical analysis.

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Anaesthesia

Sodium pentobarbital (20 mg kg^{-1} in 0.3 ml) was administered by i.p. injection. Qualitative observations indicated that the animals lost their reflexes and were unresponsive to gentle stimuli for about 2–3 h. No surgery or painful stimuli were administered. During the period of anaesthesia the rats were placed in an incubator held at a constant 32°C. When the rats had recovered, they were returned to their home cage. Control rats were not injected.

Statistical analysis

All data were compared by analysis of variance with two factors (treatment and age), with age as a repeated-measures factor. Group differences at individual time points were evaluated using the t-test.

Mortality

Four control rats and four rats from the anaesthetic group died for unknown reasons. Of the remaining rats, two rats in the anaesthetic group did not complete sufficient trials in the behavioural tasks and were excluded from the statistical analyses.

Reaction time performance

Reaction time

Figure 1A shows the change in reaction time with age. The rats responded faster with age up to the age of 18.5 months [age, $F(5,75)=6.89$, $P<0.01$], and this was similar for the two experimental groups [treatment × age, $F(5,75)=1.55$, not significant]. Individual t-tests revealed a tendency for a faster mean reaction time in the treated group in the last two test sessions ($t<1.96$, $0.05<P<0.10$).

Motor time

In contrast to reaction time, motor time did not change over the first six test sessions [age, $F(5,75)=1.07$, not significant] (Fig. 1B) and there were no differences between groups (treatment × age, treatment $F<0.89$, not significant). Motor time increased during the last three test sessions [age, $F(2,30)=213.13$, $P<0.01$], but the groups did not differ [treatment × age, $F(2,30)=2.19$, not significant].

Premature responses

The development of premature responses is shown in Fig. 1C. There were no statistically reliable differences between the groups for the first six test sessions (treatment × age, treatment $F<1.32$, not significant). However, for the last three test sessions there was a tendency for treated rats to make more premature responses than control rats [treatment, $F(1,15)=3.64$, $0.05<P<0.10$], which was due mainly to the treatment effect in the last test session [$t(15)=2.79$, $P<0.05$].

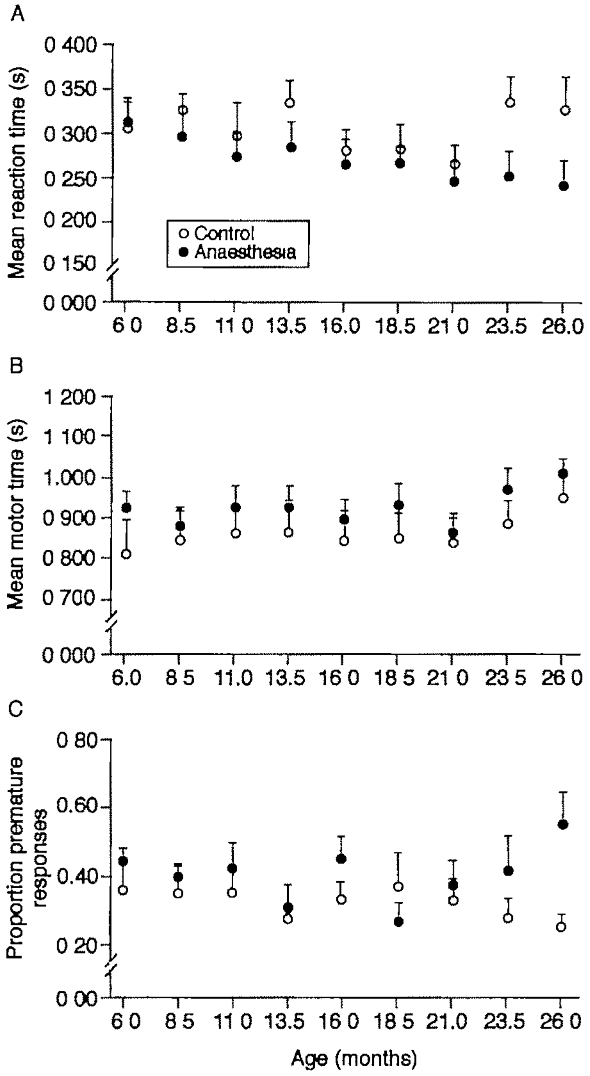

Fig 1 Performance of control and anaesthetized rats in a reaction time task tested at several time-points during their lifespan. (A) Mean reaction time. (B) Mean motor time. (C) Proportion of premature responses. Values are mean and SEM of two sessions.

Comment

We showed that repeated anaesthesia throughout life began to affect the performance of a reaction time task when the rats were over 21 months old, i.e. aged. The treated group tended to react faster than the control group during the last two test sessions. Furthermore, the anaesthesia group made more premature responses during the last test session. Faster reaction times together with an increase in errors (i.e. premature responses) is usually interpreted as increased impulsivity.[8]

Previous human studies that have shown neurological changes have noted that the observed effects may have resulted from either the anaesthetic or the accompanying surgery and the associated stress response or both.[1] No surgery was conducted on the animals in the present study and, while we cannot exclude a degree of stress, the likely cause of the observed changes was the pentobarbital.

It remains to be determined whether the effects of treatment in the present study were related to an acute effect of pentobarbital in old rats or were the result of a cumulative effect. Acute thiopental treatment did not affect the spatial memory performance in young and old rats (given the same dose of thiopental), which does not support the concept that the effects in the present study were an acute effect of treatment.[9] Moreover, in the present study the rats were not anaesthetized before the final behavioural test, when behaviour was most affected, strongly suggesting that the effects of anaesthesia are long-lasting or cumulative.

In summary, our findings suggest that repeated anaesthesia affects the behaviour of rats in the later stages of life through an increase in impulsivity. The findings support observations in studies with healthy old people[10] and aged patients[1–5] and supports the hypothesis that repeated anaesthesia is a vulnerability factor for cognitive ageing. Further studies examining the effects of different anaesthetic agents and different patterns of administration in additional animal models are indicated.

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BJA

CASE REPORTS

Grand mal convulsion and plasma concentrations after intravascular injection of ropivacaine for axillary brachial plexus blockade

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We report a patient to whom ropivacaine 1.1 mg kg^{-1} was administered for brachial plexus blockade and who developed grand mal convulsions because of inadvertent i.v. injection. No symptoms of cardiovascular toxicity occurred. Venous blood samples were taken 15, 45, 75 and 155 min after the injection. The measured total plasma concentrations of ropivacaine were 3.3, 1.6, 1.2 and 1.0 mg $litre^{-1}$ respectively. Initial plasma concentration after the end of the injection period was estimated at 5.75 mg $litre^{-1}$ using a two-compartment pharmacokinetic model.

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Brachial plexus blockade is a frequently used anaesthetic technique for surgery of the upper limb. Very often, short-acting local anaesthetics, such as prilocaine and lidocaine, are chosen because of their good safety profiles. However, in some circumstances, using a longer-acting local anaesthetic is more desirable, e.g. in vascular surgery. Ropivacaine appears to have lower cardiac and central neurological toxicity than the otherwise similar long-acting local anaesthetic bupivacaine. So far, only a few cases of severe cardiac or central neurological complications after administration of ropivacaine have been reported. Plasma concentrations associated with these side-effects have been measured in healthy volunteers but the thresholds for symptoms in patients are still controversial.[1 2] We report a case of grand mal seizure that occurred in a patient after an inadvertent intravascular injection of ropivacaine 1.1 mg kg^{-1} for axillary brachial plexus blockade. Blood samples were taken and the total venous plasma concentration of ropivacaine was determined.

Case report

A 65-yr-old male (ASA III, 90 kg, 175 cm) was scheduled for surgical revascularization of a thrombosed arteriovenous (Cimino) shunt. Significant medical history included insulin-dependent diabetes mellitus, terminal renal insufficiency and renal hypertension. He had no history of neurological or cardiac disease. Medication included insulin, nitrendipin, furosemide, metoprolol, doxazosin, sodium hydrogen carbonate and calcitriol. Before operation, the following routinely tested variables were abnormal: platelet count (119×10^9 $litre^{-1}$, normal range 150–400 $\times 10^9$ $litre^{-1}$), haemoglobin (6.7 mmol $litre^{-1}$, normal range 8.6–12.1 mmol $litre^{-1}$), haematocrit (0.30, normal range 0.40–0.54), creatinine (391 μmol $litre^{-1}$, normal range <124 μmol $litre^{-1}$) and urea (15.3 mmol $litre^{-1}$, normal range 3.6–8.9 mmol $litre^{-1}$). All other variables, including liver enzymes, electrolytes and protein concentrations, were normal. The electrocardiogram (ECG) showed normal sinus rhythm with a heart rate of 70 beats min^{-1}.

The patient did not receive any sedation before surgery. In the induction room, monitoring was placed (ECG, pulse oximetry and non-invasive arterial blood pressure) and peripheral venous access was established. The left arm was abducted at a right-angle with the forearm flexed towards the head. The skin was infiltrated with 2% lidocaine 20 mg after sterile preparation, and a 23 gauge short bevel needle with an injection line was inserted parallel and close to the

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artery and directed towards the apex of the axilla. The perivascular sheath was identified with the loss of resistance technique. No spontaneous blood flow was observed in the connected injection line. After careful negative aspiration, 20 ml of ropivacaine 0.5% was injected over 1 min in 5 ml increments, with intermittent negative aspiration. Verbal contact was made during the injection and no early signs of systemic toxicity occurred. The brachial artery was then palpated again in order to insert the needle for a second injection. Suddenly, the patient lost consciousness without any prodromal signs, such as perioral numbness or dizziness, and a grand mal seizure started. During the convulsion, heart rate increased from 70 to 80 beats min^{-1} and arterial blood pressure increased from 130/80 to 145/85 mmHg. The lungs were ventilated immediately with 100% oxygen using a mask. General anaesthesia was induced with thiopentone 400 mg, fentanyl 0.2 mg and succinylcholine 60 mg and the trachea was intubated. The convulsions stopped immediately after induction of general anaesthesia. For the following 30 min, anaesthesia was maintained with desflurane 2% in oxygen/nitrous oxide (30%/68%). ECG showed no signs of arrhythmia or changes in PQ or QT interval or QRS width. After this observation period, the scheduled surgery was performed under general anaesthesia. Three hours after the inadvertent intravascular injection of the local anaesthetic, the tracheal tube was removed. The patient had an incomplete sensory block of the ulnar nerve, evaluated by pinprick test, which lasted 4 h. The remaining brachial plexus showed no impairment of sensory function. The patient did not recall the seizure episode.

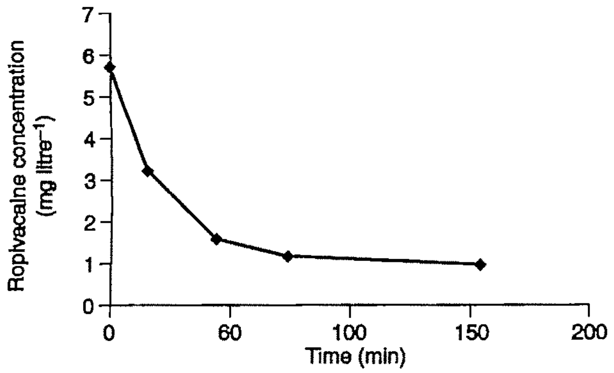

Fig 1 Total venous plasma concentration of ropivacaine. The curve was extrapolated after estimation of the initial concentration with a pharmacokinetic model.

Venous blood samples were taken 15, 45, 75 and 155 min after the injection of ropivacaine. After immediate centrifugation, plasma samples were stored at –20°C. Total plasma concentrations of ropivacaine were determined using high-performance liquid chromatography (Institute of Clinical Pharmacology, Technical University, Dresden). The linear calibration curve was validated using four samples with known ropivacaine concentrations (0.5, 1.0, 2.0 and 4.5 mg litre^{-1}). The detection limit of the method was below 0.5 mg litre^{-1} and the relative standard deviation of the method was 4.2%. The measured plasma concentrations of ropivacaine at 15, 45, 75 and 155 min were 3.3, 1.6, 1.2 and 1.0 mg litre^{-1} respectively (Fig. 1).

The peak plasma concentration immediately after the end of the injection period was estimated using a two-compartment pharmacokinetic model: $C_t = C_\alpha\, e^{-\alpha t} + C_\beta\, e^{-\beta t}$, where C_t is the plasma concentration at time point t in minutes, C_α is the concentration in the α-compartment, C_β is the concentration in the β-compartment, and α and β are the respective elimination constants. This analysis yielded an initial concentration of ropivacaine of 5.75 mg litre^{-1}. From a pharmacokinetic point of view, the available data did not allow us to discriminate between venous and arterial injection.

Table 1 Published cases of severe cardiac or neurological adverse effects after regional anaesthesia with ropivacaine N/A = not applicable; ND = not determined, NR = not reported

Regional anaesthetic technique	**Amount of ropivacaine injected**	**Plasma concentration**			**Neurological side-effect**	**Cardiovascular side-effect**	**Reference**
		Time (min)	**Total (mg litre^{-1})**	**Unbound (mg litre^{-1})**			
Interscalene brachial plexus block	2.3 mg kg^{-1}	N/A	ND	ND	Grand mal seizure	None	4
Epidural anaesthesia	2.0 mg kg^{-1}	N/A	ND	ND	Grand mal seizure	Sinus tachycardia	8
Epidural anaesthesia	0.5 mg kg^{-1}	30–40	1.4	ND	Grand mal seizure	None	9
Brachial plexus block	300 mg	N/R	2.7	0.5	Grand mal seizure	None	5
Sciatic block	2.5 mg kg^{-1}	7	3.6	0.69	Grand mal seizure	Severe bradycardia	7
		12	1.6	0.3			
Interscalene brachial plexus block	6 mg kg^{-1}	40	6.0	0.66	Minor	Arterial hypertension, sinus tachycardia	6
		60	5.4	0.49			
		80	4.6	0.41			
		98	4.0	0.27			
Brachial plexus block	4.5 mg kg^{-1}	25	4.0	0.36	Minor	Tachycardia	6
		37	2.5	0.18			
		56	2.0	0.16			

Discussion

Data regarding the incidence of seizures after brachial plexus blockade with ropivacaine are not available, but an incidence of 1.2 per 1000 blocks has been described after the use of bupivacaine.[3] Two studies investigated the thresholds for signs of minor central neurological toxicity in healthy, male volunteers by administering a continuous i.v. infusion of ropivacaine 10 mg min^{-1}.[1 2] First symptoms occurred after an infusion of 0.8–2.6 mg kg^{-1}. The corresponding total dose ranged between 62 and 160 mg and the peak total plasma concentrations measured in the venous blood samples were between 0.5 and 3.2 mg $litre^{-1}$. No severe side-effects, such as convulsions or cardiac arrhythmias, were observed. The speed of injection has a great effect on the peak plasma concentration. In clinical practice, most regional techniques are performed with infusion rates above 10 mg min^{-1}, which increases the possibility of higher peak plasma concentrations when accidental intravascular injection occurs. Therefore, plasma concentrations determined after continuous infusions in volunteers might not truly represent clinical seizure thresholds. However, the data obtained from healthy males show that seizure thresholds vary between individuals.

Cardiac or central neurological complications after the administration of ropivacaine have been described after brachial plexus[4–6] and sciatic blockade[7] and after epidural anaesthesia.[8 9] The wide range of administered doses of ropivacaine causing the symptoms confirms the inter-individual variation in threshold obtained in healthy volunteers (Table 1). Plowman and co-workers reported the onset of a grand mal seizure in a 13-yr-old boy after injecting ropivacaine 0.5 mg kg^{-1} into the epidural space.[9] The total plasma concentration of ropivacaine 30 min later was 1.4 mg $litre^{-1}$, suggesting a much larger value at the time of the incident. In our patient, we measured a total plasma concentration of ropivacaine of 3.3 mg $litre^{-1}$ 15 min after inadvertent intravascular injection, and extrapolated to a concentration of 5.75 mg $litre^{-1}$ immediately after the end of the injection period. This value is well above the venous plasma concentration of ropivacaine found to produce neurological symptoms in humans.[1] Unfortunately, we did not measure the concentrations of α-1 glycoprotein, which are known to affect the unbound concentration of local anaesthetic. Knudsen and co-workers demonstrated that the total and the unbound concentrations of ropivacaine in arterial plasma are consistently higher than the corresponding venous concentrations during and up to 20 min after an i.v. infusion.[1] After i.v. administration, the arterial circulation carries the local anaesthetic to various parts of the body, while the peripheral venous flow also returns from poorly perfused tissues. Therefore, during rapid i.v. injection the peak venous concentration probably does not represent the concentration at the site of action until equilibrium is reached.[10] In our patient, the first sample was taken 15 min after the injection and the difference, if any, between the arterial and the venous concentrations was probably minor.

Understanding the relationship between dose, body weight and speed of the systemic absorption is important in clinical practice because even a non-intravascular injection may lead to a high plasma concentration of local anaesthetic and signs of systemic toxicity.[6] The time course of the symptoms in our patient suggests that a considerable amount of the local anaesthetic had been injected intravascularly and that symptoms were not caused by systemic absorption of ropivacaine.[11] An arterial injection with a retrograde flow up to the branches of the carotid artery appears unlikely as the vascular volume of the axillary artery up to the branches exceeds the volume of local anaesthetic administered. Addition of epinephrine to local anaesthetic has been shown to identify reliably an intravascular injection if the systolic blood pressure increases more than 15 mm Hg.[12] In the present case, no epinephrine had been added to the local anaesthetic solution because the cardiovascular response to epinephrine is reduced in patients receiving β-adrenergic-blocking drugs.

Our patient showed no signs of cardiac toxicity and the changes in heart rate and arterial pressure were probably a consequence of the seizure, although a small increase in heart rate and arterial pressure has been described at similar plasma concentrations of ropivacaine.[1] In one published case, severe cardiac arrhythmias were reported in addition to convulsions. The venous plasma concentrations 7 min after the inadvertent i.v. injection of ropivacaine were similar (3.6 mg $litre^{-1}$).[7] The authors extrapolated to a peak plasma concentration at the time when the arrhythmia occurred of 7–8 mg $litre^{-1}$. This confirms that the cardiovascular system is more resistant to the effects of local anaesthetics than the central nervous system.[13]

Although brachial plexus blockade with 40 ml of ropivacaine 5 or 7.5 mg ml^{-1} has been shown to be safe,[5] administering the smallest clinically reasonable dose reduces the risk of severe toxic side-effects. Coventry and colleagues showed recently that brachial plexus blockade could be achieved with 30 ml of local anaesthetic using a nerve stimulator technique.[14] The choice of local anaesthetic is also an important issue. The short-acting local anaesthetics prilocaine and lidocaine have been shown to be safer regarding systemic toxicity. We chose ropivacaine in the present case because of its long-lasting beneficial effects on arterial and venous blood flow after brachial plexus blockade[15] and its better safety profile when compared with bupivacaine.[1 2]

In summary, we report a case of inadvertent intravascular injection of 1.1 mg kg^{-1} of ropivacaine leading to a total venous plasma concentration of 3.3 mg $litre^{-1}$. Its initial plasma concentration after the end of the injection period was estimated at 5.75 mg $litre^{-1}$ using a two-compartment model. A grand mal seizure but no symptoms of cardiovascular toxicity occurred and the patient recovered without sequelae. This case emphasizes that regional anaesthetic techniques have to be applied very carefully and that appropriate monitoring of the patient is necessary. In the absence of contraindications, the addition of epinephrine to the local anaesthetic solution should be considered in order to detect inadvertent intravascular injection.

Acknowledgements

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British Journal of Anaesthesia **87** (**5**): 787–90 (2001)

The Montgomery T-tube: anaesthetic problems and solutions

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The Montgomery T-tube is a device used as a combined tracheal stent and an airway after laryngotracheal surgery. The device is used mostly in specialist centres for head and neck surgery, and therefore, many anaesthetists may be unfamiliar with its use. The Montgomery T-tube presents the anaesthetist with challenges both during its surgical insertion when acute loss of the airway might occur and also during induction of anaesthesia in patients who have such a tube *in situ*. Anaesthetists who are unfamiliar with the tube may have to resort to ingenious ways of coping with the problems of a shared airway with a T-tube, which does not have a suitable adaptor for a standard catheter mount, as well as controlling and maintaining ventilation through the device. Safe management of such patients requires careful planning. We describe the anaesthetic management of two cases to illustrate the problems associated with Montgomery tubes.

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The Montgomery tube was introduced in the mid-1960s to support the trachea following laryngotracheoplasty. In its original form, the device is an uncuffed silicone T-tube that is inserted with the long limb in the trachea and the short limb projecting through the tracheostomy stoma (Fig. 1A and B). The T-tube is supplied in sizes from 4.5 to 16 mm (external diameter). Smaller sizes (4.5–8 mm external diameter) are available for paediatric use.[1] The tube is inserted into the upper trachea or larynx following trauma or surgery to serve as a means to maintain the tracheal airway as well as serving as a stent.

The tube itself is soft and misplacement of the upper and/or lower limbs during insertion can lead to an acute loss of airway control. In addition, there are difficulties in maintaining controlled ventilation as the extratracheal limb or the upper open end of the intratracheal portion of the tube has to be occluded to prevent loss of inspired gases and volatile agents used to ventilate the lungs. Furthermore, patients with Montgomery tubes *in situ* may present for surgery, commonly for laser application to the reconstructed airway to shave off granulomatous tissue. Unlike standard tracheostomy tubes, the Montgomery T-tube has the disadvantage of not taking standard catheter mount connectors. The anaesthetist, therefore, must devise ways of delivering volatile agents and carrier gases for general anaesthesia.

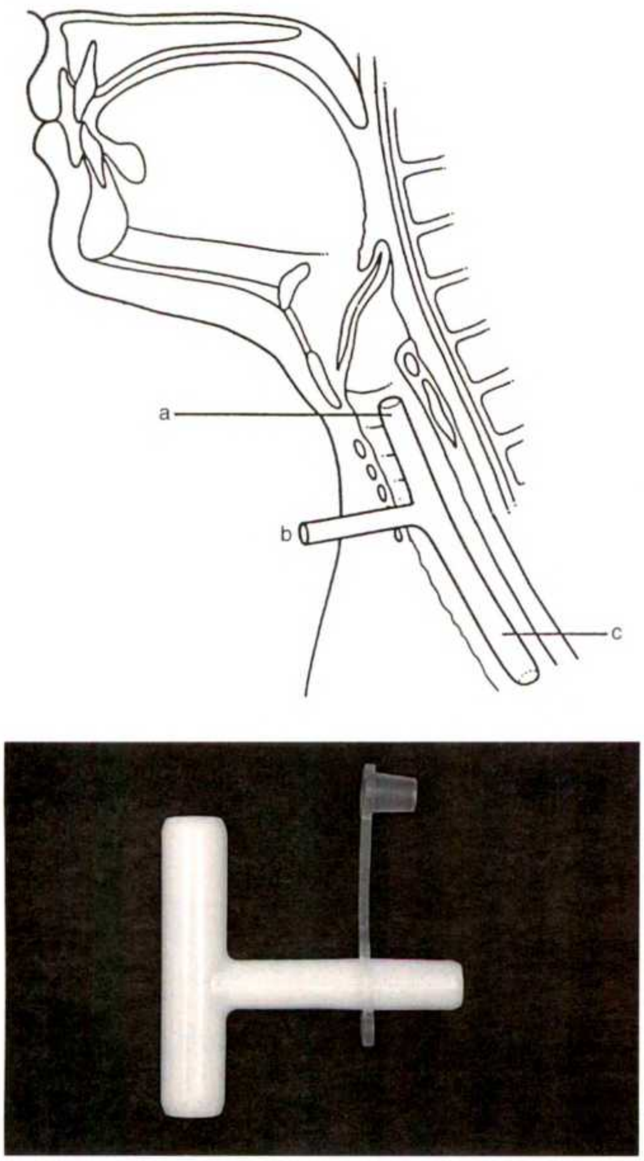

Fig 1 (A) Sagittal section of airway with Montgomery tube in place: ((a) short laryngeal part; (b) extratracheal part; (c) long tracheal part). (B) Photograph of a Montgomery T-tube.

During the management of general anaesthesia for patients undergoing laryngotracheal surgery, anaesthetists may have to deal with patients who need insertion of a Montgomery tube, or deal with cases that have such a tube *in situ*. As these cases are rare, they may present difficulties for anaesthetists who are not familiar with the tube.

We describe two cases involving the Montgomery tube, and discuss their anaesthetic management.

Case 1: insertion of Montgomery T-tube following tracheoplasty

A 24-yr-old man sustained severe skin and airway burns in a petrol explosion. As a result, he developed a high tracheal stenosis, which required a tracheostomy to relieve the airway obstruction. He was otherwise fit and well, and had no other significant medical history. He was to undergo tracheoplasty and insertion of a Montgomery tube.

He received pre-medication with 10 mg of oral temazepam and was given 0.2 mg of glycopyrrolate i.v. before induction of anaesthesia. After pre-oxygenation and institution of non-invasive monitoring, inhalation induction of anaesthesia was carried out using sevoflurane in 100% oxygen through the tracheostomy tube. Atracurium 40 mg was used for muscle relaxation and to facilitate controlled ventilation of the lungs. In order to facilitate surgery, a size 6 mm cuffed microlaryngeal tube (Mallinckrodt Medical, Athlone, Ireland) was inserted easily into the trachea through the tracheostomy stoma after the removal of the tracheostomy tube. General anaesthesia was maintained with sevoflurane, nitrous oxide, and oxygen, and supplemented with i.v. fentanyl as required. During surgery, the patient was monitored using pulse oximetry, end-tidal carbon dioxide concentration, arterial pressure, and electrocardiogram. After an uneventful tracheoplasty, a size 4 laryngeal mask airway (LMA†) was inserted in the usual manner and secured in place. The upper end of the LMA was blocked off and controlled ventilation continued using 100% oxygen through the microlaryngeal tube until the surgeon replaced it with a size 12 Montgomery tube in order to stent the tracheoplasty. Once in place, the extratracheal part of the Montgomery tube was occluded with a spigot.

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†LMA® is the property of Intavent Limited.

The anaesthetic breathing system was connected to the LMA using a standard catheter mount, and ventilation continued thereafter using the LMA. The safe and appropriate position of the upper intratracheal part of the Montgomery tube was then confirmed with a fibreoptic laryngoscope inserted through the LMA. The procedure was uneventful with satisfactory ventilation maintained throughout the operation.

At the end of the procedure, residual neuromuscular block was antagonized with neostigmine (2.5 mg) and glycopyrrolate (0.5 mg). The spigot was removed from the extratracheal portion of the Montgomery tube, and the LMA removed with the patient awake. The patient could thus breathe through both parts of the Montgomery tube.

Case 2: anaesthesia for laser application to the trachea in a patient with a Montgomery tube *in situ*

A 31-yr-old male had previously been mechanically ventilated in an intensive care unit for a month with the aid of a tracheal tube following a head injury and evacuation of a subdural haematoma. He subsequently had to undergo a laryngotracheoplasty and insertion of a Montgomery tube to treat laryngotracheal stenosis. He presented to us for laser excision of laryngotracheal granulomatous tissue with the Montgomery tube *in situ*.

Due to a compromised upper airway, an inhalation technique for induction of general anaesthesia using sevoflurane in 100% oxygen was chosen. A modified breathing system was used to anaesthetize the patient (Fig. 2). It consisted of a lightweight Bain's circuit carrying fresh gas and volatile agent to a Y-piece connection. One end of the Y-piece was connected to a facemask, the other end of the Y connection was attached to the extratracheal part of the Montgomery tube via a long catheter mount, using a suitable tracheal tube connector. A high fresh gas flow was used to compensate for the altered breathing system and to aid carbon dioxide elimination.

Following successful induction of anaesthesia, the Montgomery tube was removed and a size 6.5 mm cuffed tracheal tube covered with laser protection tape (Laser-Guard, Xomed Surgical Products Inc., Jacksonville, USA) was inserted through the tracheostomy stoma. Once the airway was secure, mechanical ventilation was carried out with the aid of atracurium to facilitate neuromuscular block. Anaesthesia was maintained with a mixture of air, oxygen, and sevoflurane. The rest of the procedure was uneventful. A tracheostomy tube was reinserted at the end of the procedure through the pre-existing stoma and ventilation continued. The patient was allowed to wake up after reversal of residual neuromuscular block using neostigmine (2.5 mg) and glycopyrrolate (0.5 mg).

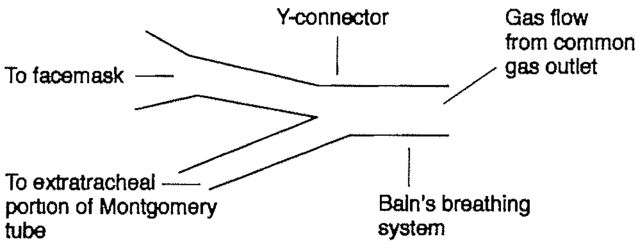
Y-connector
Gas flow from common gas outlet
To facemask
To extratracheal portion of Montgomery tube
Bain's breathing system

Fig 2 Diagram illustrating the connections between Bain's breathing system, facemask, and Montgomery tube.

Discussion

The Montgomery T-tube consists of an intratracheal part with tapered ends to minimize injury to the tracheal mucus membrane. The extratracheal stem of the T has a plug that can be used as a spigot, thus allowing normal respiration via the intratracheal part through the larynx. The tube can be used in acute tracheal injury, as a stent after tracheal reconstruction, and as a substitute for the non-reconstructible cervical trachea.[2] Due to the variable internal diameter and thickness of the tube itself, it can be difficult to predict the size of a standard 15 mm tracheal tube connector that will fit the extratracheal portion of the Montgomery tube. Therefore, a range of 15 mm connectors should be available, and it is advisable to liase with the surgical team to obtain prior information regarding the approximate size of the Montgomery tube that they wish to use.

There are a few reports about the anaesthetic management of patients who need Montgomery tube insertion.[2–5] However, there are no reports regarding the management of patients who present for anaesthesia with a Montgomery tube *in situ*.

Insertion of the Montgomery tube and airway control

The standard method of inserting the tube is to grasp it with curved haemostatic forceps and place the long intratracheal portion through the tracheostomy. The extratracheal lumen is then tugged anteriorly to straighten the tube in the trachea, and thus position the upper intratracheal limb. However, during this time the airway is not fully under control until the tube is secured in position. During insertion the tube can become misplaced or kinked below the junction of the extratracheal portion with the intratracheal part, leading to complete airway obstruction. In such cases, the Montgomery tube should be removed and reinserted appropriately. Previous descriptions of methods to overcome these problems are either too complicated or do not ensure correct placement of the Montgomery tube.

Cooper and others[3] used a rigid bronchoscope after the tracheal stoma had been created. A tape was threaded through the T-tube, and visualized through the bronchoscope after being passed through the tracheal stoma. A long forceps was then used to pull the tape superiorly and railroad the T-tube over it. This method is complicated and does not ensure adequate ventilation during the procedure.

Chonchubhair and colleagues[4] used a technique in which neuromuscular block was antagonized at the end of operation thus establishing spontaneous respiration. A gum elastic bougie was inserted through the tracheal tube. The bougie was then visualized and delivered through the tracheal stoma to the exterior. The T-tube was then railroaded into the trachea over the bougie. Once in place, the tracheal tube was advanced through the Montgomery tube, recommencing anaesthesia through the tracheal tube. This method suffers from several drawbacks. Although there is a continued presence of a tracheal tube during the insertion of the T-tube, ventilation is discontinued. There is a further risk of dislodging the T-tube and injuring reconstructed tissue during the process of advancing the tracheal tube through it and indeed, during extubation. Sichel and colleagues[5] have described a variation of this technique, using a nasogastric tube to railroad the T-tube.

Hypoventilation and air dilution of anaesthetic gases, because of the open intratracheal upper end of the Montgomery tube, were recognized by Montgomery.[1] He suggested passing a Fogarty embolectomy catheter through the extratracheal lumen up to the upper stem of the T-tube and occluding the open upper end by inflating the balloon of the catheter. A suitably sized tracheal tube could then be placed in the extratracheal lumen of the T-tube adjacent to the catheter, and ventilation continued.

In order to deal with the above problems during insertion of the tube, continuous i.v. anaesthesia and insufflation of oxygen into the lungs using a fine catheter can be used. The technique we described above offers safety and avoids the cumbersome use of catheters and railroading devices. As an LMA is inserted prior to the Montgomery tube's insertion, the airway is always under the control of the anaesthetist. Furthermore, our management of the airway does not interfere with the surgical reconstruction. Therefore, even if technical difficulties or a delay in the insertion of the Montgomery tube is encountered, the patient's safety is not put at risk. Uchiyama and Yoshino[6] have used a technique similar to the one we describe, with an important difference. They occlude the top end of the LMA, thus employing it as a means of upper airway occlusion, while ventilation continues via the extratracheal portion of the Montgomery tube. Our method not only provides a means to ventilate the patient's lungs, but also allows us to use a fibreoptic laryngoscope placed via the LMA to visually confirm the correct position of the Montgomery tube.

Anaesthesia with an in situ *Montgomery tube*

The main problem with a patient with an *in situ* Montgomery T-tube is the uncertainty regarding the volume of air passing across the tracheal stoma and that passing via the upper laryngeal end of the tube and through the larynx. Administration of a neuromuscular blocking agent at induction of anaesthesia and attempts to control ventilation under these circumstances would, therefore, be hazardous until and unless the airway is secured.

Inhalation induction of anaesthesia remains the method of choice in such patients. However, it is also necessary to supply the patient with the same composition of fresh gas flow and a volatile anaesthetic agent at both the extratracheal and laryngeal ends to prevent air dilution. We have found no description of the anaesthetic management of such patients in the literature.

We prefer to anaesthetize such patients by using a modified breathing system. A Bain's breathing system is used, and a Y-connector placed at the end of the 'circuit' splits the fresh gas flow into two streams: one to the Montgomery tube, and the other to a standard anaesthetic face mask (Figure 2). A fresh gas flow at a rate of 50 ml kg^{-1} min^{-1} is added empirically to the standard fresh gas flow requirements for the Bain's system to make allowances for our alteration. The addition of the facemask to deliver anaesthetic gases compensates for any leak around the laryngeal port of the Montgomery tube. Once the patient is anaesthetized, the Montgomery tube can be removed with gentle traction, and an appropriate laser protected tracheal tube is inserted through the tracheal stoma. If the Montgomery tube needs to be reinserted at the end of the operation, our earlier method of using an LMA is followed.

We have used these techniques for several years with good results and no adverse effects. As these patients are unlikely to present frequently, an anaesthetist who is not familiar with the Montgomery tube may be faced with difficulties. We hope that the management of these patients, which we have described above will improve safety. We also strongly suggest detailed discussions with the surgical team to avoid potential problems when dealing with a shared airway.

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Unnecessary emergency Caesarean section due to silent CTG during anaesthesia?

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We present a case of a probably unnecessary Caesarean section due to misinterpretation of the cardiotocography (CTG) trace during general anaesthesia. A 27-yr-old patient in her 30th week of an uneventful, normal first pregnancy presented with a deep venous thrombosis in the pelvic region. She was to undergo an emergency thrombectomy under general anaesthesia. During the operation, the CTG showed a lack of beat-to-beat heart rate variation (silent pattern CTG) with normal fetal heart rate. This silent CTG pattern was probably a result of the effect of general anaesthesia on the fetus. The CTG pattern was interpreted as indicating fetal distress, and an emergency Caesarean section was performed after the thrombectomy. The infant was apnoeic and had to be resuscitated and admitted to the neonatal intensive care unit. The pH at delivery was 7.23 and the baby was extubated 2 days later. Mother and child recovered without short-term sequelae. In the absence of alternative explanations, reduced fetal beat-to-beat variability with a normal baseline heart rate during general anaesthesia is probably normal.

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Surgery for non-obstetric reasons has to be performed in 1 or 2% of all pregnant women.[1 2] Intraoperative fetal heart rate (FHR) monitoring of the infant during non-obstetric surgery is controversial. Several case reports have shown that general anaesthesia influences the variability of the FHR,[3–10] but no systematic studies have been performed concerning the value of cardiotocography (CTG) monitoring during general anaesthesia for non-obstetric surgery. It is assumed that uneventful general anaesthesia providing adequate oxygenation and circulatory stability does not have any influence on the fetus.

We describe an emergency Caesarean section due to a probable misinterpretation of a silent CTG (lack of beat-to-beat heart rate variation), in a patient undergoing uncomplicated emergency vascular surgery.

Case report

A 27-yr-old female patient in the 30th week of pregnancy was to undergo emergency thrombectomy of the iliac and common femoral vein. Four weeks earlier, she had been immobilized because of pneumonia. Eight days previously her left leg had become swollen and the diagnosis of a deep venous thrombosis was made. She was admitted to hospital 2 days later because of pain in the left groin and uterine contractions and vomiting. Low molecular weight heparin treatment was started with subcutaneous nadroparinum 0.8 ml twice daily, and the contractions were controlled with oral hexoprenaline 0.5 mg four times daily combined with oral magnesium 7.5 mmol twice daily. Sonographic examination showed complete obstruction of the iliac, common femoral, and the superficial femoral vein. Because of the short time span from symptom onset and the extension of the thrombosis into the iliac vein, surgical thrombectomy was indicated, and the patient was transferred to our hospital.

The pregnancy had thus far been uneventful. The CTG the day before and on the day of surgery was normal. Because of the heparin treatment, a general anaesthetic was planned. Rapid sequence induction with thiopental 350 mg, succinylcholine 100 mg, and fentanyl 0.25 mg was performed, and anaesthesia was maintained with isoflurane in an oxygen/air mixture supplemented with fentanyl (total of 1.0 mg during the 3.5 h anaesthetic). Vecuronium 4 mg

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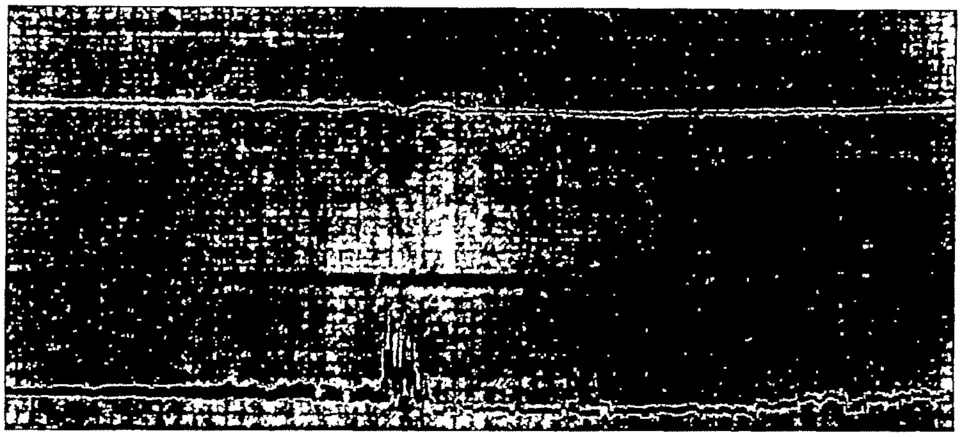

Fig 1 CTG trace recorded during anaesthesia. The upper line shows the FHR. This is constant at 150 beats min^{-1}, but without variations in baseline frequency (silent pattern). The lower line shows there is no uterine activity. The 'irregularity' in the middle of the lower trace was an attempt to disturb the child by external stimulation of the uterus; it had no effect on the FHR.

was used for muscle relaxation. After induction of anaesthesia, CTG monitoring, set up by a midwife, showed a FHR of 150/min with no variability (Fig. 1).

This CTG trace persisted throughout the operation, which took 80 min and was performed without complications. Arterial pressure and oxygenation of the mother were stable throughout. As a result of the pathological pattern of the CTG (i.e. lack of beat-to-beat variability), a senior obstetrician was consulted at the end of the thrombectomy. Neither the senior obstetrician nor the senior anaesthetist were certain about the effects of general anaesthesia on the CTG, so the CTG pattern was interpreted as fetal distress, and an emergency Caesarean section was performed. The infant was apnoeic on delivery and had to be intubated. APGAR scores of 0/2/6 at 1/5/10 min, respectively, were recorded. The pH of the umbilical vessel was normal (pH 7.23 mixed arterial/venous) indicating that the silent CTG pattern was not a result of fetal distress. The child was transferred to the paediatric ICU where she was extubated 2 days later. She recovered without apparent sequelae.

Discussion

FHR monitoring during non-obstetric surgery in the mother is controversial and may not always be possible. For instance, during abdominal operations the ultrasound probe may interfere with surgery. In a review, Rosen[11] advocates fetal monitoring whenever possible. However, Horrigan and co-workers[12] concluded that there is no documented evidence that FHR monitoring is required during non-obstetric surgical procedures in the pregnant patient, provided the mother is not hypoxic or hypotensive. The main problem during intraoperative CTG monitoring is interpretation of the CTG trace. Anaesthetic drugs have in several case reports[3–10] been shown not to alter the fetal baseline heart rate, but to decrease the heart rate variability (silent pattern). This decrease in variability may continue for up to 90 min after the mother has recovered from anaesthesia, probably because of residual concentrations of the anaesthetic agents in the fetus.[4,6,9] Usually, a 'silent pattern' in the CTG trace indicates fetal distress. If the effects of general anaesthetics on the CTG are not understood, this can, as in the present case, lead to serious misinterpretation.

Elective surgery in pregnant women is often delayed until either after delivery or at least to the third trimester, in order to maximize the chances of infant survival. However, there are still many clinical situations in which urgent surgery in pregnancy is necessary. It is assumed that apart from a slightly higher abortion rate at the beginning of pregnancy, the infant is not exposed to a higher risk and, therefore, emergency operations should not be delayed.[2,13–15] If the mother is not hypoxic or hypotensive, or if there are no other reasons for impaired uterine perfusion, a reduced fetal beat-to-beat variability with a normal baseline frequency during general anaesthesia can be regarded as normal, especially with a normal preoperative CTG.

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BJA

COMMENTARY

Pathophysiological role of the serotonin system in malignant hyperthermia

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Serotonin (5-hydroxytryptamine, 5-HT) is a biogenic amine that is distributed widely in various body tissues and cell types[1] and possesses a diversity of pharmacological effects at both central and peripheral sites. 5-HT is involved in the control of temperature regulation, cardiovascular function, muscle contraction and endocrine regulation. Peripherally, 5-HT appears to play a major role in platelet homeostasis and the motility of the gastrointestinal tract. Furthermore, 5-HT exerts important effects on skeletal muscles.

Synthesis and metabolism

5-HT is synthesized *in situ* from the amino acid precursor tryptophan. The conversion of tryptophan to 5-hydroxytryptophan is mediated by a tryptophan hydroxylase. 5-Hydroxytryptophan is subsequently decarboxylated to 5-hydroxytryptamine. 5-HT is then metabolized by oxidative deamination by the A enzyme of monoamine oxidase in the liver; the 5-hydroxyindoleacetaldehyde formed from this process is then oxidized to 5-hydroxyindole-3-acetic acid. 5-HT is stored in intracellular vesicles until depolarization of the neurone causes the release of this neurotransmitter into the synapse. Once 5-HT is released into the synapse, its function is terminated rapidly by its presynaptic reuptake into the neurone.

5-HT receptors and mechanisms of regulation

Seven major families of 5-HT receptors have been identified, all of which have distinct pharmacological properties, regional distributions and physiological functions. Most of these receptors have several subtypes (e.g. 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}).[2]

The physiological effects of 5-HT are mediated by at least four groups of 5-HT receptors, which have been distinguished pharmacologically according to the second messenger systems to which they are coupled.[1] Activation of the first group, including the 5-HT_1 and 5-HT_5 receptor subtypes, leads to a reduction in adenylate cyclase. Stimulation of the second group of receptors (5-HT_2) increases phospholipase C-β/protein kinase C activity. The 5-HT_3 receptor is a ligand-gated ion channel and activation of this group, including the 5-HT_4, 5-HT_6 and 5-HT_7 receptor subtypes, leads to increased adenylate cyclase activity. 5-HT receptors belong, with exception of the 5-HT_3 receptor, to the gene superfamily of G-protein-coupled receptors. The receptors that interact with G_s proteins stimulate the production of cyclic adenosine monophosphate via adenylate cyclase, whereas those that interact with G_i proteins inhibit the activity of adenylate cyclase. The receptors that interact with the G_q proteins stimulate phosphoinositide hydrolysis via activation of phospholipase C.

The role of 5-HT in skeletal muscles

Little is known about the role of 5-HT in skeletal muscle cells. It has been shown that 5-HT induces a concentration-dependent decrease in the rates of alanine and glutamine release from rat muscles *in vitro*.[3] Furthermore, administration of 5-HT produced an increase in the intracellular concentration of cyclic 3′,5′-AMP in these muscle preparations. These data indicate a direct effect of 5-HT on skeletal muscle metabolism via specific receptors and appear to show that the intermediary participation of muscle cyclic AMP is necessary.

Recently, evidence has become available showing that the 5-HT_{2A} receptor is expressed in rat myoblasts and that 5-HT-mediated signalling via this receptor up-regulates the expression of genes involved in myogenic differentiation

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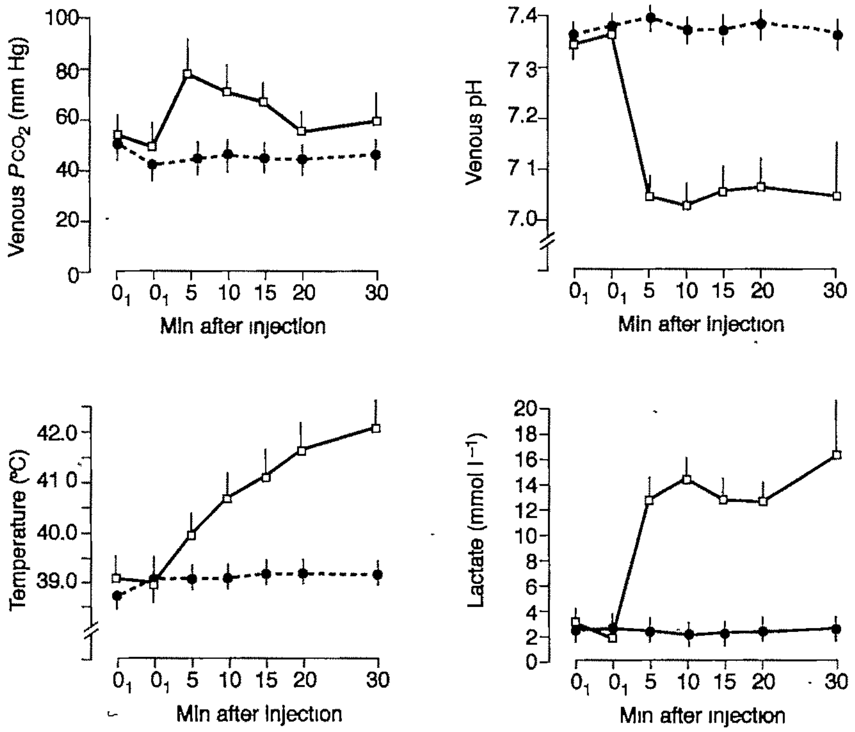

Fig 1 Metabolic responses of MH susceptible pigs (n=5; filled circles) before and after i.v. administration of saline, and after i.v. administration of DOI 0 8 mg kg^{-1} (open squares) in the same animals 2–3 days later. Data are mean and SEM (modified from reference 9).

and glucose utilization.[4] More recently, it was found that adult rat[5] and human[6] muscle expresses the 5-HT$_{2A}$ receptor and that this receptor resides exclusively in plasma membranes and not in transverse tubules.[5] The absence of 5-HT$_{2A}$ receptors in transverse tubule membranes implies that the involvement of this receptor type in excitation and contraction mechanisms is unlikely. Furthermore, it has been shown that 5-HT causes rapid stimulation of glucose uptake into muscle cells, which is mediated by the 5-HT$_{2A}$ receptor.

5-HT and malignant hyperthermia

Malignant hyperthermia (MH) episodes can be triggered in susceptible pigs by environmental stress such as exercise, heating, apprehension and excitement. Previous investigations indicate that the sympathetic nervous system is involved in porcine MH only as a secondary response. Stress significantly increases 5-HT release in the brain and circulating 5-HT levels in the blood. Furthermore, 5-HT exerts direct effects at 5-HT receptors in skeletal muscles. Thus, it has been speculated that specific serotonergic ligands may be involved in mechanisms of stress- and anaesthetic-induced MH.

In vivo studies

The 5-HT$_2$ receptor antagonist ketanserin has been shown to be effective in preventing or treating halothane- and stress-induced porcine MH.[7] Without treatment with ketanserin all MH-susceptible animals died. Ketanserin was also shown to be effective in the treatment of stress-induced hyperthermia in North American elks.[8] In this study, 18 elks were allocated randomly to receive either ketanserin or saline after induction of hyperthermia by herding them into distribution chutes and squeeze cages. After herding, the body temperature rose to 43 (1)°C and the animals hyperventilated and had a tachycardia of 111 (10) beats min^{-1}. Administration of ketanserin produced significant decreases in temperature and heart and respiratory rates, whereas in the control group values remained increased during the study period. One week later, the experiments were repeated in the same fashion but without any treatment. After this induction of stress, three of nine elks in the ketanserin group died but none of the controls not treated with ketanserin died. The deaths were explained by an excessive temperature increase (more than 45°C in the first experiment), which resulted in greater intolerance of stress during the second study period.

The results with 5-HT$_2$ receptor antagonists in the treatment of MH raised the question whether agonists at 5-HT receptors can induce MH. This has been investigated with different 5-HT$_2$ receptor agonists.[9] Administration of the 5-HT$_2$ receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) in MH pigs induced typical signs of MH, including generalized muscle rigidity with subsequent hyperthermia and marked metabolic alterations (Fig. 1).

Furthermore, administration of DOI and the partial agonist D-lysergic acid diethylamide (LSD) produced behavioural changes in conscious pigs, such as grimacing, headshakes and backward locomotion. A few minutes after injection of DOI, the MH animals exhibited mottled skin, cyanosis, hyperventilation and further symptoms of circulatory and metabolic disturbances; three of five pigs died within 60 min. In the surviving animals, the creatine kinase concentration increased from 1000 to 25 000 U litre^{-1} after 8 h. In normal pigs, stimulation of 5-HT$_2$ receptors induced transient muscle rigidity and increases in body temperature and 'psychotic' behaviour. In contrast to MH pigs, the normal pigs recovered spontaneously after about 3 h. Stimulation of 5-HT$_{1A}$ receptors with specific agonists induced behavioural changes but no signs of MH. This observation suggests that 5-HT$_2$ receptors are the site of action in 5-HT-induced porcine MH. To investigate whether the effects of 5-HT$_2$ receptor agonists were mediated through central or peripheral sites of action, the authors tested the *in vivo* effects of 5-HT, which cannot cross the blood–brain barrier. 5-HT caused mainly vomiting and diarrhoea, but also an increase in body temperature, lactate and creatine kinase levels, indicating a direct effect on skeletal muscle under *in vivo* conditions.

In further experiments, it was demonstrated that symptoms of MH were reduced or totally prevented by administration of either of the 5-HT$_2$ receptor antagonists ketanserin and ritanserin.[9] These results substantiated the idea that 5-HT$_2$ receptors are involved primarily in the induction of MH by serotonergic agents. On the other hand, it has been suggested that 5-HT is also involved in the mechanisms of MH induction by volatile anaesthetics.[10] Measurements of platelet-free and platelet-rich plasma before and during the onset of porcine MH triggered by halothane showed that physiologically active levels of 5-HT increased concomitantly with the increases in muscle tone, body temperature, venous $P\text{CO}_2$ and plasma lactate. However, it remains unclear whether these changes were induced directly by halothane or were secondary to the development of MH.

Whereas the results of the *in vivo* experiments with 5-HT$_2$ receptor agonists clearly demonstrated the involvement of the 5-HT system in MH, studies with 5-HT$_2$ receptor antagonists revealed inconsistent results. Administration of ketanserin 30 min before halothane completely prevented the induction of MH by a 12-min challenge with halothane in susceptible pigs.[7] In contrast to these findings, MH induced by a combination of halothane and succinylcholine in susceptible pigs could not be prevented by pretreatment with ketanserin.[11] Ritanserin, a potent antagonist at the 5-HT$_2$ receptor, was shown to prevent 5-HT-induced MH in pigs.[9] However, in later studies ritanserin exerted no therapeutic efficacy on halothane-induced MH in pigs.[12] Furthermore, ritanserin was ineffective in preventing anaesthetic-induced MH crises as well as halothane-mediated increases in inositol polyphosphates in MH pigs.[13] The reason for the contradictory results of these *in vivo* experiments remains unclear. Possible explanations include different durations of exposure to the trigger substances and concentrations of halothane, the additional administration of succinylcholine and the use of different breeds of pig.

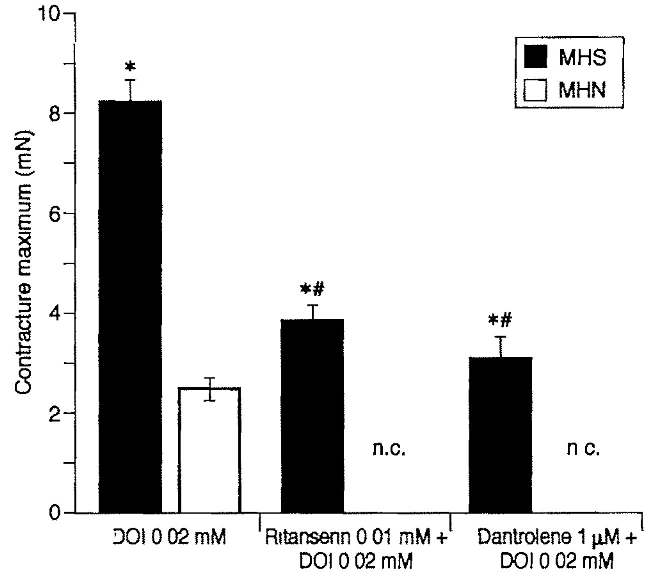

Fig 2 Maximum contracture (mN) in skeletal muscle specimens from MH-susceptible (MHS, filled bars) and normal (MHN, open bars) patients after administration of the 5-HT$_2$ receptor agonist DOI 0.02 mM with and without pretreatment with either ritanserin 0.01 mM for 10 min or dantrolene 1 µM for 10 min. Bars show mean and SEM $^*P<0.05$ *vs* normal specimens; $^\#P<0.05$ *vs* DOI; n c. = no contracture development.

In vitro studies

In vitro studies showed that the 5-HT$_2$ receptor agonist DOI induces contractures in skeletal muscle specimens from patients (Fig. 2).[14] Contractures in muscle preparations from MH patients were significantly earlier in onset and more intense than those in specimens from normal patients. In order to evaluate whether 5-HT$_2$ receptors are involved in halothane-induced MH, halothane was added to skeletal muscles pretreated with DOI. Pretreatment with DOI led to accelerated and increased development of contractures after administration of halothane only in specimens from MH-susceptible patients. Furthermore, the contracture threshold for halothane was markedly decreased after pretreatment of preparations from MH-susceptible patients with 5-HT$_2$ receptor agonists.

The *in vitro* effects of 5-HT$_2$ receptor agonists on muscle specimens from MH-susceptible patients could be reduced or completely counteracted by dantrolene[15] and by the 5-HT$_2$ receptor antagonist ritanserin.[16] Ritanserin has been shown to act also as an excellent antagonist at the 5-HT$_{1C}$ receptor. Therefore, it was speculated that the effects of ritanserin on halothane-induced contracture development could also be mediated by blockade of this receptor subtype.

Table 1 Comparison of clinical symptoms of the serotonin syndrome, malignant hyperthermia and neuroleptic malignant syndrome (NMS)

Symptom	Serotonin syndrome	Malignant hyperthermia	Neuroleptic malignant syndrome
Rapid onset	++	+++	–
Fever	++	+++	++
Muscle rigidity	+	+++	+++
Elevated creatine kinase concentration	+	+++	+++
Myoglobulinuria	+	+++	++
Rhabdomyolysis	++	+++	++
Tachycardia	+	+++	++
Haemodynamic alterations	+	++	+
Tachypnoea/hypercarbia	+	+++	++
Behavioural changes	+++	(+)	++
Altered consciousness	+++	(+)	+++
Leucocytosis	+++	–	+
Clonus	+++	–	–
Shivering	+++	–	–
Tremor	+++	–	–
Hyper-reflexia	+++	–	–

In subsequent experiments, ritanserin was shown to inhibit halothane-induced contractures in muscles from MH-susceptible patients in a concentration-dependent manner.[17]

Inositol polyphosphate system

The serotonergic effects in MH could possibly be explained by the stimulation of inositol polyphosphate (IP) metabolism via 5-HT receptors in muscle cells. The concentration of inositol-1,4,5-trisphosphate ($InsP_3$) within cells is regulated by activation of either G-protein-linked receptors or tyrosine kinase-linked receptors.[18] External signals and ligands such as 5-HT act through various membrane-spanning receptors which are coupled to phospholipase C through specific G-proteins. After stimulation, phospholipase C hydrolyses phosphatidyl-inositol 4,5-bisphosphate to give both $InsP_3$ and diacylglycerol.[19] The second messenger $InsP_3$ can stimulate Ca^{2+} release until it is deactivated by rapid dephosphorylation.

It has been proposed that alterations in signal transduction pathways and second messenger systems are intimately involved in MH. Support for this hypothesis was derived from the finding that the $InsP_3$ receptor shares considerable structural and functional homology with the ryanodine receptor.[20] Furthermore, the basal concentrations of $InsP_3$ in skeletal and cardiac muscle of MH-susceptible pigs and humans were found to be significantly elevated.[18 19] Further investigations have shown significant differences in the threshold for $InsP_3$-induced release of Ca^{2+} between MH and normal muscle fibres.[21] Exposure of MH-susceptible pigs to halothane *in vivo* caused an increase in $InsP_3$, whereas there was no effect on IP concentration in normal pigs.[22] However, ritanserin did not prevent the increase in IP concentration during halothane-induced MH in pigs.[13] This result indicates that increases in IP concentration during halothane-induced porcine MH might be due to mechanisms other than a 5-HT-mediated increase in IP synthesis. The lack of effect of ritanserin on halothane-induced MH[12] and the failure to prevent the halothane-induced increase in IP levels[13] could be related to the high dose of the trigger or to insufficient doses of ritanserin used in the *in vivo* experiments. The latter hypothesis is supported by the fact that the ritanserin doses used for the *in vitro* studies were 2- to 20-fold higher than in the *in vivo* experiments.

Serotonin syndrome

The serotonin syndrome is caused by excessive 5-HT availability in the CNS at the 5-HT_{1A} receptor. There may also be interactions with dopamine and 5-HT_2 receptors. The serotonin syndrome is most commonly induced by high doses of serotonergic drugs leading to an excessive increase in the intrasynaptic 5-HT concentration.[23] Serotonin syndrome has also been observed after recent discontinuation of an 5-HT-enhancing drug of long half-life, the effects of which were still present.[24] Numerous other drugs, including inhibitors of 5-HT metabolism, 5-HT receptor agonists and drugs increasing 5-HT release (e.g. cocaine), induce serotonergic overactivity.

The clinical manifestation of the serotonin syndrome consists of rapid onset of cognitive–behavioural changes, neuromuscular abnormalities and dysfunction of the autonomic nervous system (Table 1). The appearance of a body temperature above 40.5°C usually signals a severe disease process with significant mortality and complication rates.

Treatment of the serotonin syndrome is initiated by discontinuation of serotonergic drugs and in most cases all symptoms disappear within 24 h. In patients with persistent symptoms and/or increasing severity, administration of antiserotonergic drugs to block postsynaptic 5-HT receptors may be considered. Pharmacotherapeutic management also includes benzodiazepines, propanolol and dantrolene. Symptomatic treatment, including cooling, institution of muscle relaxation and mechanical ventilation, may also be required.

Despite the remarkable clinical similarities between serotonin syndrome, neuroleptic malignant syndrome and MH (Table 1), there are important differences in aetiology, clinical course and treatment. MH is induced by the action of volatile anaesthetics and succinylcholine on skeletal muscle cells, whereas serotonin syndrome is induced by the central stimulation of serotonergic receptors and neuroleptic malignant syndrome by blockade of dopamine receptors. The main features of the serotonin syndrome (behavioural changes and altered consciousness) are only rarely observed in MH. In MH the only effective pharmacological treatment is the administration of dantrolene.

Conclusions

The pathophysiological role of the 5-HT system in the regulation of skeletal muscle function and Ca^{2+} release in MH is yet to be defined. Results of *in vivo* studies in MH-susceptible pigs have shown that agonists at 5-HT receptors are capable of initiating the MH syndrome. MH induced by 5-HT receptor agonists is totally prevented by 5-HT receptor antagonists, but these antagonists were ineffective in most cases in the treatment of anaesthetic-induced MH. The results of *in vitro* experiments in skeletal muscle preparations from MH patients with 5-HT receptor agonists and antagonists provide evidence that 5-HT is also involved in the mechanisms of MH in humans. On the basis of the findings of these investigations, it is suggested that a functionally or structurally altered 5-HT system might be involved in the development of MH.

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Correspondence

How can we improve the outcome of oesophagectomy?

Editor—We read the article by Tandon and colleagues,[1] and the accompanying editorial[2] with interest, and would like to raise a number of points.

The authors contend that improved anaesthetic and perioperative care could make an important difference to morbidity and mortality in these patients, specifically by improving management of one-lung ventilation, and more intensive monitoring pre-, intra- and postoperatively. What the authors do not address, however, is the type of operation performed, and the impact this may have on intraoperative and postoperative complications.

At our institution, surgeons have recently published their experience,[3] having performed 1085 transhiatal oesophagectomies without thoracotomy between 1976 and 1998. Seventy-four per cent of patients had cancer and 24% benign disease. The hospital mortality rate was 4% (4.5% for cancer patients) below the reported 5–8.8% in large UK centres, with long-term survival equal to or exceeding that reported for the transthoracic approach. Postoperative respiratory complications were reported in less than 2%, and were mostly limited to pneumonia or atelectasis prolonging hospital stay beyond 10 days. Of the 44 deaths in the series, three were due to intraoperative bleeding, and only five were due to postoperative respiratory failure. In our experience of over 140 transhiatal oesophagectomies in the last year, acute respiratory distress syndrome (ARDS) appears to be a rare problem, as the anastomosis is performed in the cervical region with 'side to side' stapling. Anastomotic breakdown is unusual (3% rather than the 13% quoted),[1] is relatively easy to manage, and is unlikely to precipitate ARDS.

From an anaesthetic standpoint, transhiatal oesophagectomy is a much simpler procedure. Our patients are admitted on the morning of surgery. 'Optimization' consists of an incentive respirometer for 2–3 weeks preoperatively, with instructions to stop smoking and to walk 2 miles a day during that period in order to condition themselves physically for surgery and early ambulation. Our anaesthetic management consists of general anaesthesia with a single lumen rather than a double lumen tracheal tube (DLT), and a thoracic epidural for postoperative analgesia, with standard monitoring and an arterial line. One or two large bore peripheral lines are inserted. The anaesthetic is given by a second year resident with a consultant supervising two operating rooms. At the end of surgery, patients are extubated and taken to the recovery room, from where they are sent back to the thoracic ward, bypassing ITU/HDU altogether. Blood loss averages less than 700 ml, surgical time is 3.5 h, transfusion is rare, and inotropes are almost never used. Length of hospital stay averages 7 days.

In this institution, we have seen that transhiatal oesophagectomy with preoperative optimization consisting of exercise and the cessation of smoking, combined with a cervical anastomosis and a thoracic epidural, have eliminated the need for a DLT, and postoperative intensive care. Postoperative anastomotic breakdown remains the most important factor in the development of ARDS, and simply by avoiding an intrathoracic anastomosis, this complication can be virtually eliminated. Other surgical issues, such as the need for emergency re-exploration for bleeding, and transfusion requirements, are beyond our control as anaesthetists. Rather than investigating new anaesthetic strategies, perhaps our efforts to improve outcome would be best served by changing the operation!

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Editor—I wish to thank Leon Visser and Bruce Martin for their interest in my editorial and their contribution to this debate. They have quoted the hospital mortality from transhiatal oesophagectomy operations performed at the University of Michigan Medical Center between 1976 and 1998. During this time the average number of oesophagectomy operations was 49 per year and the hospital mortality was 4%; this result is commendable. They also quote an exceptionally low morbidity; for example a less than 2% incidence of reported postoperative respiratory problems. Their morbidity appears lower than any previously published. Were there any failures in definition, detection or documentation of postoperative complication? The problems with retrospective analyses, particularly data quality, are well known.

Accepting their shortfalls, reviews of the literature can be a valuable guide. In 1999, Rindani and colleagues[1] presented descriptive comparisons for 2675 transhiatal (THO) with 2808 Ivor-Lewis (ILO) oesophagectomy operations performed between 1986 and 1996. The 30-day mortality rate was 6.3% for THO and 9.5% for ILO. Postoperative morbidity was similar for respiratory complications (24% for THO, 25% for ILO), and cardiovascular complications (12.4% for THO, 10.5% for ILO). Transhiatal oesophagectomy patients appeared to have a higher incidence of anastomotic leaks (16% for THO, 10% for ILO), anastomatic strictures (28% for THO, 16% for ILO), and recurrent laryngeal nerve injuries (11.2% for THO, 4.8% for ILO). Rindani and colleagues also referenced two comparative prospective randomized studies; these did not demonstrate a difference in outcome between the two techniques.[2 3]

From their experience, Visser and Martin recommend that anaesthetists should work at changing the operation. I think that for an anaesthetist to prescribe the operation to a surgeon is as unsound as the surgeon dictating the anaesthetic. As anaesthetists, we need to be aware of factors other than the 30-day mortality and morbidity. The long-term survival figures following oesophagectomy remain poor, and only approximately 25% of patients survive 5 years. This outcome also needs to be addressed. The final plan for the operation, knowing the operability and resectability of a tumour in an individual patient, is probably best formulated by the multidisciplinary care team. Surgical considerations are part of that process and include the surgical experience, site of the tumour, a palliative or curative operation, and blunt dissection *vs* lymph node or *en-bloc* resection. The complexity of the surgical decision-making is well-illustrated in a somewhat dated (1990), but nevertheless valuable, review by

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Muller and colleagues[4] of 130 papers comprising 79 911 patients who had undergone an oesophagectomy for cancer. I believe that by continuing our endeavours to improve anaesthetic strategies we will help more patients to survive the postoperative period and have the opportunity to achieve their long-term goals.

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1 Rindani R, Martin CJ, Cox MR. Transhiatal versus Ivor-Lewis oesophagectomy: is there a difference? *Aust N Z J Surg* 1999; **69**: 187–94
2 Goldminc M, Maddern G, Le Prise E, Meunier B, Campion JP, Launois B. Oesophagectomy by a transhiatal approach or thoractomy: a prospective randomized trail. *Br J Surgery* 1993; **80**: 367–70
3 Chu KM, Law SY, Fok M, Wong J. A prospective randomized comparison of transhiatal and transthoracic resection for lower-third esophageal carcinoma. *Am J Surg* 1997; **174**: 320–4
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Editor—We thank Visser and Martin for their comments, which relate to details of the sugical procedure performed in our study, and will respond briefly to each point

First, the purpose of our study was to determine perioperative factors associated with acute lung injury, and particularly adult respiratory distress syndrome, following transthoracic oesophagectomy for cancer. It was not to discuss or compare the main types of surgical approach available, namely transthoracic and transhiatal oesophagectomy. Only a few prospective randomized controlled trials have addressed this issue, with insufficient patient numbers and with conflicting results. When the world literature between 1986 and 1996 was reviewed, including Visser and Martin's own series of transhiatal oesophagectomies, overall morbidity and specifically respiratory complications (24% *vs* 25%) were similar for transhiatal and transthoracic oesophagectomy.[1] Postoperative mortality was also similar. However, it is of interest to note that anastomotic leakage was more common following transhiatal oesophagectomy (16% *vs* 10%).

Although we recognize that Visser and Martin's institution has great expertise using a transhiatal approach, we wish to clarify the references to their recently reported experience.[2] The morbidity and mortality quoted relate to a series with a very different case mix from ours, with a high proportion of their patients undergoing oesophagectomy for benign disease (in fact 26% rather than the 24% suggested in Dr Visser's letter). Whilst they suggested that the anastomotic leak rate has been low during the last year, their overall leak rate for the series is published as 13%, and is certainly not a complication that has been 'eliminated'. The average blood loss was under 700 ml However this specifically excluded nine patients with massive intraoperative haemorrhage (between 5850 and 18 440 ml), three of whom died intraoperatively. There were no intraoperative deaths in our series using the transthoracic approach.

They are also fortunate to have a referral population who are 'able to walk 2 miles a day in order to optimize themselves prior to major surgery'. Our patients from the North East of England were predominatly elderly, with significant co-morbidities and a history of cigarette smoking, placing them in high category on peroperative risk stratification.

Finally and importantly, there are real concerns regarding the appropriateness of transhiatal oesophagectomy as a 'cancer clearing' operation as it precludes a formal mediastinal lymphadenectomy. There is now evidence that this may not only be associated with a higher loco-regional recurrence rate but may also compromise long-term survival for some patients.[3] This may partly account for their actuarial 5-year survival of 23% following transhiatal oesophagectomy for carcinoma.[2] compared to our published overall 5-year survival of over 30%.[4]

Despite improvements in perioperative care, oesophagectomy is still associated with a high incidence of respiratory complications and a significant in-hospital mortality. The association we have demonstrated between intraoperative instability and postoperative course suggests the need for prospective studies of pre- and intraoperative cardiorespiratory optimization. This information opens new avenues and offers a further opportunity to improve the overall outcome for patients with oesophageal cancer. Based on current evidence, neither short- nor long-term outcome would be improved by changing to a transhiatal procedure.

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1 Rindani R, Martin CJ, Cox MR Transhiatal versus Ivor-Lewis oesophagectomy: is there a difference? *Aust N Z J Surg* 1999; **69**: 187–94
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Perioperative risk factors for acute lung injury following elective oesophagectomy

Editor—We read with interest the article by Tandon and colleagues about the perioperative risk factors for acute lung injury following elective oesophagectomy[1] and the accompanying editorial by Sherry.[2] In a retrospective analysis of 168 patients undergoing oesophagectomy, Tandon and colleagues identified a number of factors associated with the development of adult respiratory distress syndrome (ARDS) post oesophagectomy. Factors found to be associated with the delopment of ARDS included: a history of smoking, volume of fluids, use of inotrope and vasoconstrictors, intraoperative hypoxaemia, intraoperative hypotension, duration of surgery, the experience of the surgeon, and postoperative anastomatic leak. The strongest association was with the development of a postoperative leak. Sherry in her editorial argues that respiratory complications are a legitimate surrogate marker for outcome and are linked to the amount of hypoxaemia during one-lung ventilation She questions whether anaesthetists with infrequent experience of the use of double lumen tubes avoid their use during oesophagectomy and place more reliance on lung retraction.

It is possible, in our view, that the risk factors identified by Tandon and colleagues are, at least in part, risk factors for the development of postoperative anastomotic leaks and that the ARDS observed by them developed secondary to an undiagnosed leak in at least some of their patients. As discussed by Sherry, postoperative leaks are difficult to diagnose and the diagnosis may be missed or the magnitude of the leak underestimated. A diagnosis of an anastomotic leak has been reported in up to 15% of patients undergoing oesophagectomy.[3,4] However, a radiological diagnosis of a leak on contrast swallow can be made in 32% of patients who have undergone oesophageal surgery.[5] Further radiology may, and in our experience frequently does, miss leaks.[6] Smoking, volume of fluids infused, use of inotrope and vasoconstrictors, intraoperative hypoxaemia, intraoperative hypotension, duration of surgery and the experience of the surgeon are all factors that could be anticipated to affect the incidence of anastomotic leak.

We reviewed 233 consecutive patients undergoing oesophagectomy under the supervision of one surgeon over a 7-year period, most patients receiving the care of a single anaesthetist. There were 14 deaths, either in hospital or within 30 days of surgery (6%). Two patients sustained fatal myocardial infarctions and one died from a pulmonary embolism. The remaining 11 patients all developed ARDS prior to death but in only one patient was a specific cause for ARDS not identified. The other 10 patients all developed serious postoperative complications which we consider triggered their lung injury (gastric necrosis in four, aspiration in two, haemorrhage and massive transfusion in two, chylothorax in one, and hepatorenal failure in one). There were no intraoperative concerns over hypoxia in any of our patients who developed ARDS, nor were intraoperative inotropes administered to any patient.

We have increasingly recognized, as have others,[7] that intrathoracic anastomotic problems may elude initial detection on contrast swallow radiology. In addition, this investigation is not always available to patients who have developed ARDS and are receiving intermittent positive pressure ventilation. We have a preferred policy of early re-operation for suspected or confirmed anastomotic problems and have identified 14 (6%) patients who have developed an intrathoracic leak. In all cases the leak was due to a variable degreee of necrosis of the proximal tubularized stomach. Four patients in this group died (28%). In managing these often very sick patients, we feel we have diagnosed a reversible primary cause for the ARDS, but label the complications as being due to an anastomotic problem rather than ARDS from an unidentified cause.

We agree that ARDS following oesophagectomy has a high mortality rate and any anaesthetic strategy that may decrease the occurrence of this complication warrants investigation. We have, however, not been able to show a correlation between intraoperative hypoxaemia and fatal ARDS. We would suggest that any anaesthetic strategy that compromised surgical access such as using a tracheal tube may increase the incidence of post-oesophagectomy complications because of increased lung retraction and impaired operating conditions. We suggest that all patients undergoing oesophageal surgery should receive the same expert thoracic anaesthetic care; if this is not available, the patient should be referred to a large volume centre where this thoracic anaesthetic experience is available.

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1 Tandon S, Batchelor A, Bullock R, *et al.* Peri-operative risk factors for acute lung injury following elective oesophagectomy. *Br J Anaesth* 2001; **86.** 633–8

2 Sherry KM. How can we improve the outcome of oesophagectomy? *Br J Anaesth* 2001; **86**: 611–13

3 Muller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. *Br J Surg* 1990; **77**: 845–57

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5 Tanomkiat W, Galassi W. Barium sulphate as contrast medium for evaluation of postoperative anastomotic leaks. *Acta Radiol* 2000, **41**: 482–5

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7 Sauvanet A, Baltar J, Le Mee J, Belghiti J. Diagnosis and conservative management of intrathoracic leakage after oesophagectomy. *Br J Surg* 1998; **85**: 1446–9

Editor—Thank you for the opportunity to respond to the letter of Pennefather, Page, Shackcloth and Russell. I must first comment that the list of factors they quoted, those that were associated with the development of acute respiratory distress syndrome (ARDS), were from the univariant analysis which was then used for the subsequent multiple logistic analysis. Some of these factors did not achieve significance in the multiple logistic analysis, and so they may be misleading in the weight they have been given here

Pennefather and colleagues appear to suggest that postoperative anastomotic leak be used as a marker for adverse outcome after oesophagectomy operations. All oesophageal surgeons and anaesthetists recognize that postoperative anastomotic leak carries a high risk and are active in the detection and treatment of it, as are Pennefather and his colleagues. However, postoperative anastomotic leak, albeit carrying a high mortality rate, is not a good surrogate marker for adverse outcome. It is notoriously difficult to diagnose and often missed.[1] ARDS is the final common pathway for many postoperative complications including anastomotic leak, is by far the most common ultimate cause of death following oesophagectomy, and is easy to diagnose. Since not all patients that develop ARDS die, by using it as a surrogate marker for adverse outcome the study population can be smaller.

Pennefather and colleagues doubt whether operative hypoxaemia is associated with the development of ARDS, because they had no concerns about oxygenation in those of their patients who went on to develop ARDS. Nevertheless, Tandon and co-workers[2] in their analysis did identify an association.

Finally, they suggest transferring those patients who need an oesophagectomy to a large volume thoracic centre. There are 2000 oesophagectomy operations performed in the UK each year and upper gastrointestinal (GI) surgeons who are trained and have a special interest in oesophageal disorders do the majority of them. These surgeons often work in units that specialize in oesophageal cancer and other oesophageal disorders, and oesophagectomy is only one of the oesophageal procedures they perform. Specialized diagnostic and intervention radiologists, histopathologists, oncologists, upper GI nurses and others support them. It would be inappropriate to transfer a patient from this environment of expertise to another for the sake of the anaesthetic.

From the figures presented by Pennefather and colleagues, their experience is an average of 33 oesophagectomies each year. This is similar to other specialized upper gastrointestinal units, but still equates to less than one per week. Experienced anaesthetists are capable of recognizing those areas within their own practice that need updating. I continue to encourage anaesthetists with infrequent practice in the techniques for one lung anaesthesia to keep up-to-date with current research and consider ways to increase their experience as necessary, perhaps by visiting thoracic units and by discussing problems with colleagues. If they have concerns about the use of a double-lumen tube in any patient, then the use of single lumen tube, its risks and benefits, is an option that should be considered by the anaesthetist and their surgeon; it does have precedent.[3]

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1 Tanomkiat W, Galassi W Barium sulphate as contrast medium for evaluation of postoperative anastomotic leaks. *Acta Radiol* 2000; **41**: 482–5
2 Tandon S, Batchelor A, Bullock R, *et al* Peri-operative risk factors for acute lung injury following elective oesophagectomy. *Br J Anaesth* 2001; **86**: 633–8
3 Tachibana M, Abe S, Tabara H, *et al* One-lung or two-lung ventilation during transthoracic oesophagectomy? *Can J Anaesth* 1994; **41**: 710–5

Editor—In reply to Pennefather and colleagues, the main purpose and conclusion of our study was to demonstrate that relatively subtle intra-operative events, likely to be associated with changes in tissue perfusion, may ultimately contribute to post-oesophagectomy morbidity and mortality. In this respect, respiratory complications and ARDS were a marker of poor outcome

A traditional view of anaesthetic leaks is that they are caused by sub-optimal surgical technique. While surgical skill is undoubtedly of great importance to outcome, our study raises the interesting possibility that peri- and postoperative tissue ischaemia may also contribute to complications. In this context, the findings of Dr Pennefather's team are not surprising. Anastomotic leak is more likely to occur in the face of tissue ischaemia.

Pennefather states that his group were unable to find evidence of intraoperative hypoxaemia associated with complications. Did they use our area under the curve method? The hypoxaemia that we detected is not gross and only becomes apparent following mathematical manipulation of the intraoperative data. A simple visual inspection of anaesthetic charts is unlikely to show the changes which we detected.

We fully agree that a very high level of anaesthetic skill is required to successfully manage these patients and this is most likely to be available in centres frequently performing this procedure.

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Diagnostic confusion caused by dapsone-induced methaemoglobinaemia

Editor—We read with interest the report by Falkenhahn and colleagues[1] describing a case of acute severe methaemoglobinaemia secondary to dapsone overdose. We would like to report our own case in which dapsone-induced methaemoglobinaemia was a cause of diagnostic confusion.

A 47-year old female was admitted to the Accident and Emergency department complaining of an asthma attack. She had a past history of brittle asthma requiring numerous hospital admissions. One episode necessitated artificial ventilation. She was taking dapsone for longstanding dermatitis herpetiformis. On examination she was anxious, dyspnoeic, afebrile and had generalized cyanosis. Her heart rate was 130 beats min^{-1} and arterial pressure 170/100 mm Hg. Her respiratory rate was 25 bpm with good air entry bilaterally and only minimal expiratory wheeze in the right upper zone. Pulse oximetry showed a haemoglobin saturation of 76% with a good trace. Acute severe asthma was suspected and nebulized bronchodilators and i.v. aminophylline therapy were initiated. The anaesthetist was summoned as the admitting physician felt that the patient may require ventilatory support. Arterial blood taken for analysis was noted to be 'dark in colour' but the results were pH 7.392; $P\text{o}_2$ 24.43 kPa; $P\text{co}_2$ 3.58 kPa; HCO_3 19.5 mmol litre^{-1}; BE$^-$ 6.1 mmol litre^{-1} and $S\text{a}_{\text{O}_2}$ 99.4%. The anaesthetist, puzzled by the apparently conflicting low pulse oximeter saturation and high PO_2 together with the relative well-being of the patient, suspected dyshaemoglobinaemia. Co-oximetry revealed a methaemoglobin level of 19.7%. This level was compatible with the clinical features of the patient.[2,3]

Further questioning of the patient revealed that she had recently been self-prescribing dapsone for a flare up of her dermatitis herpetiformis. During the preceding 24 h she had taken 500 mg (6.0 mg kg^{-1}). The recommended dose is 1–2 mg kg^{-1} 24 h^{-1}. In view of the diagnosis of methaemoglobinaemia, the patient was transferred to the high dependency unit, and given high flow oxygen via face mask. The asthma treatment was withdrawn. Activated charcoal was given to prevent further absorption of dapsone from the gastrointestinal tract. Consideration was given to treatment with methylene blue, but a blood sample taken 2 h after admission showed the methaemoglobin level had fallen to 17% with an improving clinical picture. Twenty-four hours after admission, the methaemoglobin level was 8% and she was discharged from hospital.

We feel that this case highlights some important learning points. It demonstrates that the importance of taking a detailed and accurate history should never be underestimated. As anaesthetists, our training encompasses the principles of spectrophotometry and this allows us to understand both its benefits and limitations With the widespread use of pulse oximetry, this case serves as a reminder that not all instances of oxygen desaturation are cardiorespiratory in origin.

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1 Falkenhahn M, Kannan S, O'Kane M. Unexplained acute severe methaemoglobinaemia in a young adult. *Br J Anaesth* 2001; **86**: 278–80
2 Elonen E, Neuvonen PJ, Halmekoski J, Mattila MJ. Acute dapsone intoxication. A case with prolonged symptoms *Clin Toxicol* 1979; **14**: 79–85
3 Ferguson AJ, Lavery GG. Deliberate self-poisoning with dapsone. A case report and summary of relevant pharmacology and treatment *Anaesthesia* 1997; **52**: 359–63

Editor—I would like to thank Lewis and Clark for their interest in our case report.[1]

Diagnostic difficulties due to methaemoglobinaemia as a result of concurrent dapsone medication have been reported both in emergency[2,3] and non-emergency situations.[4,5] This is most often due to the 'cyanosis' produced by methaemoglobin, which becomes more significant if the patient has a history of coexisting respiratory illness. However, patients with low levels of methaemoglobin can be asymptomatic,[4] and are often diagnosed by the pulse oximeter showing an apparently spurious reading. Due to the use of dapsone for various skin conditions and as prophylaxis against *Pneumocystis carinii* pneumonia,[2] it has been more commonly reported as a causative agent. The patient in our case report was found to have severe methaemoglobinaemia but she denied ingestion of any drugs. It was only after gas chromatography/mass spectrometry of the urine sample that a qualitative match with dapsone was identified. The authors rightly point out that although arterial blood gas analysis and co-oximetry confirm the diagnosis, taking a careful history can avoid confusion especially in the presence of severe respiratory symptoms.

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1 Falkenhahn M, Kannan S, O'Kane M. Unexplained acute severe methaemoglobinaemia in a young adult. *Br J Anaesth* 2001; **86**. 278–80

2 Ward KE, McCarthy MW Dapsone-induced methaemoglobinaemia. *Ann Pharmacother* 1998; **32**: 549–63

3 Seaton RA, Nathwani D, Kirk J, France AJ. Blue and breathless. *Hosp Med* 1999; **60**: 530

4 Chawla R, Kundra P, Bhattacharya A. Asymptomatic methaemoglobinaemia and its implications. *Acta Anaesthesiol Scand* 1998; **42**: 736–8

5 Mayo W, Leighton K, Robertson B, Ruedy J. Intraoperative cyanosis: a case of dapsone-induced methaemoglobinaemia. *Can J Anaesth* 1987; **34**: 79–82

Cancellation of hypertensive patients

Editor—I read with interest the results of the survey by Dix and Howell.[1] I am an English trainee currently working in the public health system in Perth, Western Australia. I have recently surveyed all 75 anaesthetists within the department, 24 trainees and 51 consultants. We perform 15 000 general anaesthetics per annum at The Royal Perth Hospital. The number of cancellations due to hypertension for elective surgery made in the last year was only 15 on the day of admission. Our cancellation rate is therefore low in comparison to the UK rates of 1–27%. Our system of admission differs from the UK in that all patients are seen by an anaesthetist in pre-admission clinic, except for cardiothoracic patients. The patients are then admitted on the day of surgery to a preoperative area. This area at The Royal Perth Hospital is certainly one that I would consider contributing to 'white coat hypertension'. It is next to the main corridor in the hospital and patients are often seated in gowns prior to entry to the operating theatre suite. The management of the hospital is pushing this system forward in efforts to reduce costs.

Why then are our cancellation numbers due to hypertension so low? The practices of the 75 anaesthetists surveyed about their management of hypertension did not differ in the main from Dix and Howell's study,[1] with greater than 95% of them agreeing in principle to the protocol laid out recently by Prys-Roberts.[2] One has to conclude that pre-assessment clinics contribute to the low rate of cancellations due to hypertension, and are perhaps one way forward in overcoming this problem, as the introduction of protocols for such management remains a conflicting issue.

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1 Dix P, Howell S. Survey of cancellation rate of hypertensive patients undergoing anaesthesia and elective surgery. *Br J Anaesth* 2001; **86**: 789–93

2 Prys-Roberts C. Isolated systolic hypertension: pressure on the anaesthetist? *Anesthesia* 2001, **56**: 505–10

Editor—We read Dr Onslow's letter with interest and are grateful for her comments. We have no doubt that a preoperative assessment service based around a group of anaesthetists who are consistent with regard to their management of hypertension is a good thing. A consistent practice within the unit must help to reduce uncertainty and confusion among surgical and nursing colleagues and reduce the risk of patients receiving conflicting messages with regard to their management.

We agree that the flow diagram provided by Professor Prys-Roberts offers a useful approach to the management of hypertension in the perioperative period.[1] In our paper we stated our view that there is little evidence to support deferring anaesthesia and surgery in patients who, at presentation for surgery, are found to have blood pressure readings consistent with stage one or stage two hypertension. That is to say a systolic blood pressure between 140 and 179 mm Hg and/or a diastolic pressure between 90 and 109 mm Hg However, we are not persuaded by Prys-Roberts' suggestion that it is acceptable to undertake anaesthesia for elective surgery in patients with isolated systolic hypertension and admission blood pressures of up to 210 mm Hg.

Systolic blood pressures of between 180 and 210 mm Hg are consistent with stage 3 hypertension. The evidence on perioperative risk in patients with stage 3 hypertension is limited, and to a considerable extent decisions have to be based on extrapolating from studies of medical patients. These suggest that raised systolic pressure is a cause for concern. Data from the Framingham heart study domonstrate positive associations between systolic blood pressure and pulse pressure and coronary heart risk, while a negative association was found between diastolic pressure and coronary heart risk.[2] Patients with raised blood pressure associated with anxiety (a situation that Prys-Robert particulary identifies with markedly raised systolic pressure) have been shown to have an increased incidence of altered left-ventricular structure and function.[3] With regard to the perioperative setting, there is evidence for an increasing incidence of postoperative myocardial ischaemia with increasing blood pressure such that patients with systolic blood pressure of 180 mm Hg are three times more likely to suffer postoperative myocardial ischaemia than those with a preoperative systolic blood pressure of 120 mm Hg.[4]

Much of this evidence was reviewed by Prys-Roberts. However, we are more cautious than he is in our conclusions regarding the management of patients with stage 3 hypertension, including isolated systolic hypertension. We would recommend deferring anaesthesia and surgery in these patients, where possible, to allow the blood pressure to be treated.

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1 Prys-Roberts C. Isolated systolic hypertension pressure on the anaesthetist? *Anesthesia* 2001; **56**. 505–10

2 Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham heart study. *Circulation* 1999; **100**: 354–60

3 Muscholl MW, Hense HW, Brockel U, Doring A, Riegger GA, Schunkert H. Changes in left ventricular structure and function in patients with white coat hypertension: cross sectional survey. *BMJ* 1998; **317**: 565–70

4 Howell SJ, Hemming AE, Allman KG, Glover L, Sear JW, Foex P. Predictors of postoperative myocardial ischaemia. The role of intercurrent arterial hypertension and other cardiovascular risk factors. *Anesthesia* 1997; **52**. 107–11

Is it safe to artificially ventilate a paralysed patients through a laryngeal mask?

Editor—I read with interest the well-balanced discourse on the subject of ventilation through a laryngeal mask.[1] However, I feel that the calculation contained in the final paragraph deserves some comment.

The authors state 'one might expect about 16 deaths each year in the UK from aspiration of gastric contents' when using the above technique in 'about 4 million anaesthetics'. The number of deaths is derived from the product of: (i) the observed incidence of aspiration with the LMA†;[2] and (ii) the observed mortality of confirmed pulmonary aspiration.[3] First, the incidence of gastric aspiration reported by Verghese and Brimacombe[2] involved the evaluation of the laryngeal mask not only in paralysed patients but also in spontaneously breathing patients. This does not help us to answer the original question stated in the title of the editorial.

Second, the observed mortality reported by Warner and colleagues[3] is derived from a database compiled before the introduction of the LMA. It is interesting to note that there is a higher incidence of pulmonary aspiration in this dataset compared with the previously mentioned study in which only laryngeal masks were used.[2]

Finally, the implication of the calculation is that there would be an *extra* 16 deaths should this anaesthetic technique be universally adopted. Every anaesthetic technique will have a profile of associated morbidity and mortality, however, most will carry with them certain discrete advantages. This may well be true for the technique in question and its advantages should be harnessed by careful patient selection.

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1 Sidaras G, Hunter JM. Is it safe to artificially ventilate a paralysed patient through a laryngeal mask? The jury is still out. *Br J Anaesth* 2001; **86**: 749–53
2 Verghese C, Brimacombe J. Survey of laryngeal mask airway usage in 11 910 patients: safety and efficacy for conventional and nonconventional usage *Anes Analg* 1996; **82**: 129–33
3 Warner MA, Warner ME, Weber JG. Clinical significance of pulmonary aspiration during the perioperative period. *Anesthesiology* 1993; **78**: 56–62

Editor—Thank you for the opportunity to reply to Dr MacKillop's letter. In the calculation of morbidity, we aimed to stimulate more thought and discussion about the use of the LMA. We did indeed state that 'one might expect about 16 deaths each year in the UK from aspiration of gastric contents, when using the above technique in about 4 million anaesthetics'. This calculation is a theoretical exercise, but we suggest that such complications are under-reported, and thus that our prediction may, if anything, be less than the real value.

Unfortunately, Verghese and Brimacombe[2] did not specify in their paper how many patients had received neuromuscular blocking agents during artificial ventilation through an LMA. The patients in their study were mainly undergoing elective surgery, although some may have been emergencies. However, in the absence of a large and much needed study comparing the incidences of gastric aspiration in spontaneously breathing and artificially ventilated patients through the LMA, we had no alternative but to use Verghese and Brimacombe's results.

Warner and colleagues[3] in the Mayo Clinic collected a very large morbidity database associated with positive pressure ventilation through a tracheal tube. As we stated in our editorial, none of these patients were anaesthetised using an LMA. This study demonstrated that, if a tracheal tube was used, all complications associated with pulmonary aspiration occurred before intubation or after extubation, but none when the patient was intubated. As Dr MacKillop rightly observed, there was a higher incidence of pulmonary aspiration in this dataset. The population for this study did, however, include many more emergency patients who would have a higher risk of aspiration than in Verghese's study.

We are anxious to discourage artificial ventilation through an LMA in emergency patients who, for abdominal surgery, require a neuromuscular blocking drug. We are also concerned that insufficient deliberation is given to using such an anaesthetic technique in other patients at risk of pulmonary aspiration, for example, the obese.

The LMA offers several advantages, but it can not replace a tracheal tube, when safety is paramount. Morbidity associated with gastric aspiration is a serious complication, and we agree with Dr MacKillop that careful selection is required in the choice of anaesthetic technique for an individual patient. We cannot, however, support his attitude that we must accept a degree of morbidity and mortality with any anaesthetic technique. On the contrary, we believe any new technique should only be used if such problems are reduced. To tolerate anything less is, in our view, unacceptable

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1 Sidaras G, Hunter JM. Is it safe to artificially ventilate a paralysed patient through a laryngeal mask? The jury is still out. *Br J Anaesth* 2001; **86**. 749–53
2 Verghese C, Brimacombe J. Survey of laryngeal mask airway usage in 11 910 patients: safety and efficacy for conventional and nonconventional usage. *Anes Analg* 1996; **82**: 129–33
3 Warner MA, Warner ME, Weber JG. Clinical significance of pulmonary aspiration during the perioperative period *Anesthesiology* 1993; **78**: 56–62

An unusual case of airway obstruction

Editor—We would like to report an unusual case of airway obstruction, which could have led to serious consequences.

A 74-year-old lady on the day surgery urology list for cystodiathermy was anaesthetised using propofol and fentanyl. After easy insertion of a laryngeal mask airway (LMA†) manual ventilation was attempted since the patient remained apnoeic. This proved almost impossible to achieve. The LMA was removed and ventilation was attempted using an oral airway and facemask, which again proved unsuccessful. The patient was immediately intubated with an 8-mm tracheal tube (ETT), with a grade 1 laryngoscopic view and again could not be ventilated. External inspection of the anaesthetic circuit did not reveal any obvious obstruction but no breath sounds were audible on clinical examination She was disconnected from the circuit and an AMBU bag was tried, without success Since her oxygen saturation had now decresed to 60% expired air was blown into the ETT without an intervening filter. This resulted in chest wall movements Ventilation was then assisted directly with the AMBU bag with prompt return of the oxygen saturation to 100%. The patient recovered from this incident without any sequelae and surgery was deferred for a future date.

Closer examination of the breathing circuit revealed the presence of a transparent plastic disc inside the neck of the 15M-22F connector between the Filta Therm Heat and Moisture Exchanging Filter (HMEF) and the flexible catheter mount

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†LMA® is the property of Intavent Limited

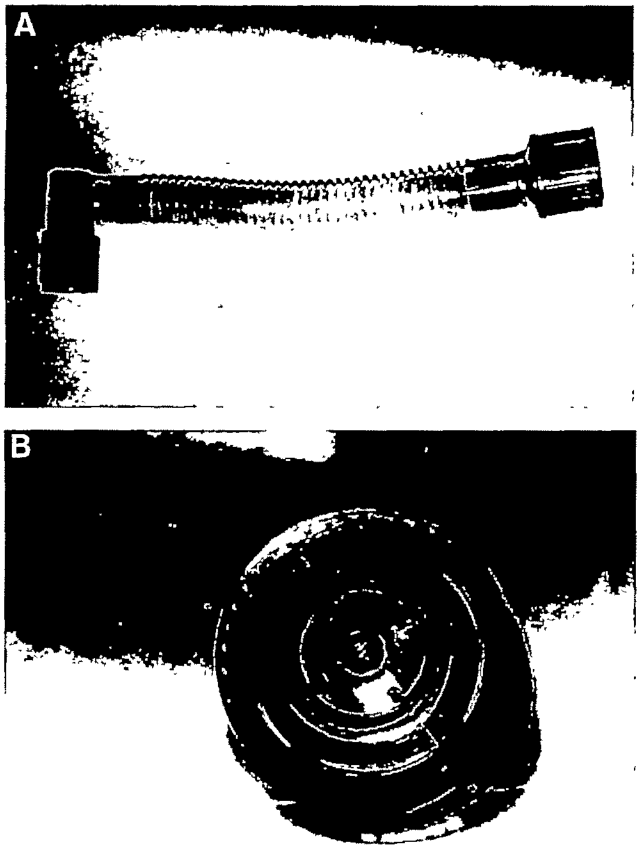

Figure 1 (A) The flexible catheter mount (B) Close up view of the occluding plastic disc within the neck of the catheter mount

(Intersurgical complete respiratory systems) which is supplied as a single unit (Fig. 1A and B). This was responsible for the obstruction. The anaesthetic equipment was tested prior to the start of the operating list according to the Association of Anaesthetists guidelines.[1] The disposable catheter mount with the attached HMEF had not been part of the routine circuit testing. The equipment check even if it had been performed with the offending item in circuit would not have identified the obstruction. Infection control guidelines preclude connecting the circuit without an intervening filter. With hindsight we could have identified the obstruction by feeling for the gas flow, or by performing a sniff test.[2] The manufacturers of the catheter mount were informed of this incident immediately and were very prompt in withdrawing the possibly affected lot from circulation by issuing an urgent advisory note. A similar episode was reported without any harm coming to the patient,[3] but more recent incidents involving catheter mount obstructions, one of them causing the death of a child, have generated a lot of concern and have been widely reported in the press.[4]

Various causes of airway obstruction exist in the operative environment. When an obstruction is recognized, a systemic approach to diagnosis and treatment must be implemented. Hosking and colleagues[5] have proposed a practical algorithm for the management of airway obstruction. The first step is for the patient to undergo manual ventilation with the reservoir bag to remove the ventilator as a source of obstruction. The second step, in the event of continued obstruction, should distinguish between circuit and ETT causes. ETT obstruction can be ruled out by passing a suction catheter or by successful direct ETT ventilation. If direct ETT ventilation is successful, then the circuit comes under suspicion. When the circuit and ETT have been eliminated as causes, patient sources of resistance such as bronchospasm, pneumothorax or pulmonary oedema must be considered. In this case, the ETT and the patient were eliminated as causes of obstruction when ventilation was restored by direct ETT ventilation.

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1 Association of Anaesthetists of Great Britain and Ireland. *Checklist for Anaesthetic Apparatus.* London: AAGBI, 1997
2 McDonald D. To sniff or not to sniff. *Anaesthesia* 1993, **48**. 928
3 Thomas R, Finch S. A blocked catheter mount. *Anaesthesia* 2001; **56**: 88
4 The Times. Oxygen pipes and the death of a nine-year-old. *http://www.thetimes.co.uk/article/0,,8-2001272649,00.html*
5 Hosking MP, Lennon RL, Warner MA, *et al.* Endotracheal tube obstruction: Recognition and management. *Mil Med* 1989, **154**: 489–91

Rocuronium: high risk for anaphylaxis?

Editor—We read with interest the discussions regarding anaphylactic and anaphylactoid reactions to neuromuscular blocking agents.[1–3] Rose and Fisher indicate that the number of reactions to rocuronium appears to be related to the market share for the product. The surveys that have been reported in publications from France[4 5] are contradictory. Levy and colleagues identify the problem of potential false positive reactions with skin tests that may have led to an overestimation of reactions attributed to rocuronium in France. Indeed, biases and influences which determine whether or not a reaction is being tested for and reported, and the differences in specificity and sensitivity of diagnostic tests, may lead to substantial deviations in the perceived risk for reactions to compounds. This is magnified by the fact that the reactions are relatively rare.

An alternative and possibly more objective approach to looking at severe reactions during anaesthesia is to retrospectively investigate the anaesthesia charts for signs that could be an indication of a severe reaction. At the anaethesia department of our hospitals, intraoperative anaesthetic data have been gathered for many years using an automated system. These data include cardiovascular variables such as sequential recordings of blood pressure and heart rate as well as oxygen saturation data. Using these databases, with more than 100 000 patients, we have selected only adult patients who received a muscle relaxant as

Table 1 Rocuronium: high risk for anaphylaxis

		Number of events (%)		
Neuromuscular blocking agent	Number of patients (n)	Systolic BP <70 mm Hg	Heart rate >140 beats min^{-1}	Oxygen saturation <90%
Atracurium	7162	0.15	0.07	0.06
Pancuronium	2210	0.14	0.81	0.32
Rocuronium	29057	0.08	0.07	0.06
Succinylcholine	3344	0.00	0.12	0.12
Vecuronium	5522	0.09	0.04	0.11

part of the anaesthetic procedure. We calculated the incidence of decreases in blood pressure and oxygen saturation and increases in heart rate for the different neuromuscular blocking agents used in these hospitals. A quick analysis selecting only sustained deviations for a period of at least 10 min, within 5 min of administering the relaxant, is shown in Table 1.

The above results should not be confused with the occurrence of true anaphylactic and anaphylactoid reactions. However, the results do give an indication of the incidence of clinically important episodes of changes in cardiovascular and respiratory variables during anaesthesia with different relaxants (but not necessarily due to these relaxants). Since the data are automated and objective, these figures are not influenced by the possible biases involved in the current testing methods and reporting systems. Our figures support the conclusion of Rose and Fisher, that there is no cause for concern with regard to the incidence of anaphylaxis with rocuronium. In the clinic, rocuronium appears to be as safe if not safer than other NMBAs.

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1 Rose M, Fisher M. Rocuronium: high risk for anaphylaxis? *Br J Anaesth* 2001; **86**: 678–82
2 Neal SMcD, Manthri PR, Gadiyar V, Wildsmith JAW. Histaminoid reactions associated with rocuronium. *Br J Anaesth* 2000; **84**: 108–11
3 Levy JH, Gottge M, Szlam F, Zaffer R, McCall C. Weal and flare responses to intradermal rocuronium and cisatracurium. *Br J Anaesth* 2000; **85**: 844–9
4 Laxenaire MC. Epidemiology of intraoperative anaphylactic reactions, fourth survey (1994–1996). *Ann Fr Anesth Reanim* 1999; **18**· 796–809
5 Laxenaire MC, et Le Groupe d'Etudes des Reactions Anaphylactoides. Epidemiology of intraoperative anaphylactic reactions. *Ann Fr Anesth Reanim* 1999; **18**[Supp;. 1]: 86S

Perioperative bradycardia

Editor—I was pleased that Kinsella and Tuckey concluded their response to my commentary[1] on their review paper[2] by highlighting the common ground between us, that is in regard to 'the imperative on ensuring venous return during high regional anaesthesia, and of continuous close perioperative monitoring'. However, in their analysis of the possible mechanism of bradycardia during high spinal anaesthesia they have made an assumption that is incorrect. The clear statement in their letter is that they believe that perioperative bradycardia is always reflex in origin. One of the points I was trying to make in my commentary is that this may not always be the case. Hypoxia in the presence of an intact nervous system will produce tachycardia and hypertension through reflex mechanisms. However, the direct effect of hypoxia on the heart is depression, so in the presence of sympathetic block a progressive bradycardia will occur. I would accept that some parasympathetic activation may be involved also, but I did not intend to suggest (as they assume) that a chemoreflex is involved. Neither would I suggest that this mechanism was necessarily the one involved in all cases described by Caplan and colleagues,[3] but it is important that a full analysis of all the possibilities is considered in such cases.

Finally, they ask why positive pressure ventilation with 100% oxygen did not produce a positive response in the patients in Caplan and colleagues' series. I would suggest a simple explanation: it was applied too late.

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1 Wildsmith JAW, Kinsella SM, Tuckey JP. Perioperative bradycardia. *Br J Anaesth* 2001; **87**: 671
2 Kinsella SM, Tuckey JP. Perioperative bradycardia and asystole. relationship to vasovagal syncope and the Bezold-Jarisch reflex. *Br J Anaesth* 2001; **86**: 859–68
3 Caplan RA, Ward RJ, Posner K, Cheney FW. Unexpected cardiac arrest spinal anaesthesia: a closed claims analysis of predisposing factors *Anesthesiology* 1988; **68**: 5–11

British Journal of Anaesthesia 87 (5) 807–9 (2001)

Book Reviews

Pharmacology of the Critically Ill. Gilbert Park and Maire Shelley (editors). Published by BMJ Publishing Group, London. Pp. 189; indexed; illustrated. Price £27.50. ISBN 07279 12216.

This short book is the most recent addition to the evolving series, *Fundamentals of Anaesthesia and Acute Medicine*. The two editors are highly respected intensivists from the UK, but the contributing chapters are written by authors from Canada, Switzerland, Australia and New Zealand as well as England and Ireland. The book's main aim is to enhance understanding of the principles of pharmacology in the critically ill patient, rather than to act as a textbook of therapeutics. This is clearly stated in the preface and applies to most of the book, although a few authors fall into the trap of writing about the pharmacology of treating the critically ill patient.

The editors explain why this book is necessary: first, the increasing complexity of organ failure in today's intensive care patient population is associated with increasingly complex pharamacokinetic and pharmacodynamic profiles; and second, the increasing degree of polypharmacy prescribed for critically ill patients can only increase the risk of adverse drug interactions.

The book begins with a well-written and pithy reminder of the principles of basic pharmacology and drug action. It also includes details of potential postgraduate examination favourites such as chirality, prodrugs and the importance of preservatives. The chapter ends with a clear summary of drug measurement techniques including radio-immunoassay, enzyme-linked immunosorbent assay, and high performance liquid chromatography. At this early stage, the book's clarity makes it obvious that it is written for clinicians.

The next chapter explores pharmacokinetics and pharmacodynamics in more detail and explains how these are influenced by commonly occurring conditions (pyrexia, systemic inflammatory response syndrome, hypoxia) in critically ill patients. The author of the next chapter offers a comprehensive account of drug receptors but admits that the data supporting this chapter are derived from healthy individuals rather than critically ill patients.

Renal failure is probably the best understood organ failure in terms of influencing pharmacology, and is discussed next. There is a full account of how the majority of drugs used in intensive care and anaesthesia are affected by renal dysfunction and renal replacement therapy. There is also an important mention of how renal disease alters hepatic drug metabolism. The following chapter on liver failure is realistic in that it discusses the influence of relatively commonly occurring conditions, such as 'ITU jaundice' and ischaemic hepatitis, on pharmacology as well as discussing fulminant hepatitis.

The section on heart failure is comprehensive in that it not only addresses altered pharmacokinetics resulting from the associated decrease in hepatic and renal perfusion, but also includes an account of how the failing heart responds differently to certain drugs. The chapter on gut failure discusses how mucosal oedema, increased mucosal permeability and hypoperfusion can influence pharmacology. However, the author strays into therapeutics when he comments on the benefits of enteral feeding. The next author makes the same error in that his chapter about brain failure is mostly a therapeutic account. Despite this, the chapter is well written and informative.

In contrast, the next author makes the greatest effort at promoting the main aim of the book. The chapter on respiratory failure deals exclusively with how respiratory failure affects pharmacology, and does not attempt to deal with the pharmacological therapy for this condition at all. The chapter on paediatric pharmacology emphasizes the dictum that children must not be treated as small adults. The final chapter is about safe prescribing and concludes the book on a positive note in offering a common sense approach to drug prescribing for the critically ill patient.

In summary, this was a difficult book to plan but the editors have done very well in ensuring that it achieves its goal, for the most part. There is a small degree of disharmony introduced by the many different writing styles, but this is largely unavoidable in a book with multiple authorship. This book will be of interest to all practising intensivists and will be particularly useful to those intending to take postgraduate examinations in critical care medicine and anaesthesia At £27.50, it represents reasonable value and will make a valuable addition to any departmental library

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Total Intravenous Anaesthesia. Nicholas L. Padfield (editor). Published by Butterworth-Heinemann, Oxford. Pp. 306. ISBN 0-7506-4171-1.

Only a few books on i.v. anaesthesia offer a clear translation from the pharmacologial theory of i.v. agents to clinical guidelines that are understandable and useful for every anaesthetist. This concise book portrays the history, pharmacological background and clinical application of i.v. anaesthesia and sets the first step in the translation to clinically meaningful guidelines It is aimed at residents in anaesthesia and practising anaesthetists. In 17 chapters, divided into three sections, Nicholas Padfield has brought together the submissions of 15 specialists in this field.

The first section consists of introductory chapters on the history and development of total i.v. anaesthesia, the pharmacology of the drugs used, the administration of i.v. anaesthesia, and the drug interactions that one may encounter. While reading these first chapters one is struck by the differences in the quality of information offered. Dr Padfield starts with an accurate account of how and when i.v. anaesthesia became a recognizable entity, mentioning the inception of the UK Society for Intravenous Anaesthesia and the introduction of new short-acting agents.

The next two chapters update us on the pharmacology of drugs and drug interactions in a superficial, fragmental manner. Especially, the chapter on drug interactions fails to distinguish between pharmacokinetic and dynamic interactions and between pharmacokinetic interactions and interpatient pharmacokinetic variability. The last two chapters of this section relate to the pharmacokinetics of infusion and the practical aspects of the administration of total i.v anaesthesia. They both offer the clinician a thorough body of knowledge on the background of total i.v. anaesthesia as well as a good set of practical guidelines that will improve the success of its clinical application. Again, I am unsure why the editor has included a description of the use of one-syringe drug mixtures of propofol with alfentanil or ketamine. The use of these one-syringe mixtures neglects the differences in pharmacokinetics between the agents used and can only lead to under- or over-dosing of one of the two agents. This practice does not allow for an improvement in patient care and thus should not be advocated.

Section 2, entitled 'Specific Issues', handles the issues of anaesthetic depth monitoring and the problem of postoperative nausea and vomiting in a very readable and point-to-point manner.

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The strength of this book lies in Section 3, which goes into detail on the practical application of total i.v. anaesthesia for specific procedures such as day case, cardiac, ENT, and neurosurgery. Although the description of the pharmacology of the various i.v. agents is repeated more than once, these chapters offer valuable and detailed information for those of us who wish to apply total i.v. anaesthesia for a specific procedure, or in a specific patient population. The chapters in this last section reveal the 'pros' and 'cons' of the use of specific agents for that procedure or in that specific patient with ready-to-use dosing guidelines. The book finally ends with an overview of the current and future developments in this area of anaesthetic practice.

In conclusion, although the chapters on the theoretical background of i.v. anaesthesia are not always that strong, this book offers valuable information on the practical aspects of total i.v. anaesthesia. I would recommend the book to residents in anaesthesia and to those who have not yet had contact with total i.v. techniques

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Clinical Notes for the FRCA. 2nd Edn. Charles D. Deakin. Published by Churchill Livingstone. Price £19.95. ISBN 0-443-06403-2.

This is the second edition of a popular book. It has encompassed some new developments in anaesthesia and has additional chapters on trauma management, major incident management, systemic inflammatory response syndrome, opioids, renal replacement therapy, and ecstasy. There has also been some revision of existing chapters from the first edition.

Each section in the book covers a system, for example Cardiovascular, or a topic such as Intensive Care. The information is presented as a series of notes and key points. The candidate preparing for the Final FRCA who has a good background knowledge of the subject will find this format a useful *'aide mémoire'* when revising. The book has the advantage of being compact and in softback, for carrying about and referring to during the working day Many candidates may prefer to work from their own notes, but this book is laid out with many lists and tables that an individual could annotate as required.

This is not a textbook in the sense that it only gives outlines of the subjects it covers. It is well referenced and the information is accurate and lends itself well to the structured *viva* format of the Final FRCA. The range of the book is enormous and it is perhaps for this reason that the expert in an individual area might find it to be a little behind on the latest, most up to date theories, and a little sketchy in places. This is inevitable with the turn around of information in the 21st century. Notwithstanding this criticism, the standard is, overall, very good.

One of the most useful features of this book is the reproduction of a number of guidelines and recommendations from various august bodies. Whilst most anaesthetists will be familiar with the guidelines from our own College and Association, the inclusion of, for example, the guidelines from the British Thoracic Society on the management of acute, severe asthma in adults and children is most valuable. The final chapter of the book lists and enumerates current anaesthetic guidelines, and references the appropriate chapters where they have been presented in full. Reports of Joint Working Parties with the College of Ophthalmologists, and Radiologists, and with the Department of Health are also included. A section of this chapter is also given over to the NCEPOD reports, and to the 1998 Confidential Inquiry into Maternal Deaths. Summary information and recommendations from all of these reports are included.

The book therefore contains much useful information for the teacher as well as the candidate. The notes could be used for tutorial outlines as well as for revision notes. The useful summaries and guidelines are of value to any anaesthetist, and having them collected together saves much time in searching the literature. The book has a useful appendix consisting of the syllabus for the Primary and Final FRCA together with the examination regulations.

In summary, this book will be useful to examination candidates, but will also find wide application for all anaesthetists in their clinical and educational work.

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Manage Your Pain. Michael Nicholas, Allan Molley, Lois Tonkin, Lee Beeston. Published by ABC Books, Sydney. Pp. 224; illustrated. Price Aus $27.40. ISBN 07333 0883X.

Chronic pain represents a major cause of suffering and it is estimated that some 10% of the population may suffer from this distressing condition at some stage. Management of patients with persistent chronic pain requires a multidisciplinary team approach to elicit specific physical or psychological aetiologies and plan appropriate therapy; however, for many patients with ongoing chronic pain there is no specific treatment available. In such situations, pain management programmes have been proven to be very highly effective in reducing the extent of subjective pain, improving mood and activity, and often reducing the extent of medication taken by sufferers, albeit without affecting the underlying cause of the chronic pain. This book describes a cognitive pain management programme developed at the Pain Management and Research Centre at the Royal North Shore Hospital in Sydney, Australia. This particular programme is termed ADAPT (Active Day Patient Treatment) and represents an intensive 3-week day course. It is based on initial work in which one of the senior authors, Mike Nicholas, collaborated whilst working as a psychologist at St. Thomas' Hospital, London in 1998 before he moved to Sydney.

This book has been couched in the vocative and is designed to be read by patients, and relatives of chronic pain sufferers. It describes the causes of chronic pain and how it differs from acute pain, what treatment options are available, and the role of different specialities in the management of pain. It then goes on to discuss how patients should pace themselves to overcome the effect of chronic pain on activities, how to set goals with stress on the benefit of physical activity and its improvements, the value of positive thinking, and avoidance of negative thoughts or even catastrophizing. In addition, it discusses distraction techniques, problem solving, personal relationships, and how to maintain improvements by dealing with setbacks, stress, and return to normal social and work activities.

Recently, I was privileged to spend a short sabbatical at the Pain Management Centre at the Royal North Shore Hospital, Sydney and shadowed a group of patients through a 3-week pain management programme. It was an extremely impressive demonstration of the value of cognitive behavioural therapy delivered with humanity, humour, and a huge dose of down-to-earth common sense. I recall musing at the time that much of the teaching in the course would be of inestimable benefit in every school curriculum; indeed, it would be of greater value in learning how to cope with the vicissitudes of life than most other aspects of childhood education.

This book should have a universal appeal. I recommend it unreservedly not only to patients with chronic pain, but also to all medical undergraduates in addition to non-specialist clinicians likely to encounter patients with the distressing problem of chronic pain.

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Brain Death. E. F. M. Wijdicks (editor). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 223. ISBN 0-7817-3020-1.

In the past few years much media attention has been focused on brain death and artificial support of organs in the face of catastrophic brain injury. This book is also coming out at a time when public confidence in the UK has unfortunately been assuaged from the merits of organ donation as part of the fall-out of recent adverse medical publicity. The appearance of this plain sky-blue hardback suggests it to be a turgid and impenetrable read but the opposite is true—it is a fascinating exploration of the multiple facets of this controversial topic. Also, the premise of the book is far more personal and emotional than the cover suggests—it is dedicated: 'to all who faced the worst loss but gained by giving life to others'. The author is an American neurologist and the book is a collection of 10 chapters contributed by fellow American colleagues, mostly neurologists. In interesting contrast, in the British Isles, the diagnosis of brain death falls mainly under the remit of intensivists and anaesthetists, the anaesthetic state being a *'pharmacologically induced reversible coma'*. The chapters consider cultural, religious, philosophical, ethical and legal aspects of the subject as well as the pathophysiology. All this is preceded by an absorbing canter through the historial perspective, which traces the evolution of the neurological criteria used for establishing brain death after the invention of the mechanical ventilator.

Wijdicks starts with a look at 'Le Coma Depasse', the landmark article by Mollart and Goulon in *Revue Neurologique* (1959), which for the first time asks the most critical ethical question: 'Do we have the right to stop resuscitation using criteria that pretend to know the boundary of life and death?' Wijdicks describes the uneasiness surrounding a new problem; organ donation for transplantation from patients in vegetative states. An editorial in the *Journal of the American Medical Association* in 1968 written by Appel, former president of the American Medical Association opened: 'Might not the overenthusiastic heart surgeon be tempted to declare the donor dead before death occurred in order to have a viable heart to transplant?'

The most beneficial section is that dealing with the differential diagnoses of brain death. Throughout the book it is appreciated that the diagnosis of brain death relies on clinical examination and not on technology. The chapter on legal aspects of brain death is particularly informative for those among us who know little about such issues and are ignorant of how medicine and the law interact It emphasizes the use of well-defined criteria, rigorous documentation, and prioritizing communication with families. The chapter looking at religious and cultural aspects details differing religious beliefs and attitudes to brain death and gives an appendix of the views of 29 religious denominations regarding brain death, organ donation and transplantation. In chapter nine, Bernat analyses the misleading nature of the term 'brain death' with the implication that other forms of death exist. He goes on to explore the philosphical and ethical matters of brain death, discussing issues such as maternal brain death and preservation of the live fetus The dedication 'to all who faced the worst loss but gained by giving life to others' almost becomes a *'declaration of interest'* by the final chapter, which is about organ procurement and preparation for transplantation. This is obviously a subject of great importance to the author and one he feels deserves more attention with the current mismatch between organ supply and demand.

The book is aimed at all personnel involved in the diagnosis of brain death, organ procurement and transplantation, though in reality parts of the book have potentially a far broader audience ranging from general practitioners and paediatricians to bereavement counsellors. It serves as interesting reading and also as a reference text.

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Guide to Contributors

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

Papers for publication and all editorial communications should be addressed to: Dr J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005. E-mail: bja@liv.ac.uk

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Investigations, and Short Communications) but not for Reviews, Case Reports, or Commentaries. It should give a a succinct account of the problem, in up to 250 words. It may be used as it stands by abstracting journals. References are not used in this section, except in exceptional circumstances.

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The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

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Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

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When a drug is first mentioned it should be given the international non-proprietary name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

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Description of results, while concise, should permit repetition of the investigation by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. Significance should be given as values of probability.

Discussion

The discussion should not merely recapitulate the results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially. Individuals named must be given the opportunity to read the paper and approve their inclusion in the acknowledgements, before the paper is submitted.

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There should be a list of references at the conclusion of the paper, commencing on a new sheet.

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Chapter in a book:

2. Hull CJ. Opioid infusions for the management of postoperative pain. In Smith G, Covino BG, eds. *Acute Pain* London: Butterworths, 1985; 155-79

Monographs:

3. Moore, DC *Regional Block*, 4th Edn. Springfield, Illinois Charles C. Thomas, 1979

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We interrupt this to bring you a very important message:
By the time you've read this, someone will have died from sepsis.

Recent analyses conducted by ICNARC (the Intensive Care National Audit & Research Centre) on data collected from 92 adult general ICUs[†] have shown that the prevalence of severe sepsis[‡] during the first 24 hours in the ICU is 27.7%[§,1]. In England and Wales (excluding Northern Ireland and Scotland), this figure potentially represents a prevalence of 21,033[§,1] severe sepsis cases during the first 24 hours in the ICU out of a total adult general ICU caseload of 73,203[§,1].

Severe sepsis is a major cause of morbidity and mortality. In adults, severe sepsis has been associated with mortality rates ranging from 28% to 50%[2] and these rates have remained unchanged for several decades. For the 92 adult general ICUs included in the Case Mix Programme Database, the associated overall hospital mortality for severe sepsis in England, Wales and Northern Ireland is 44.7%[§,1].

Lilly Critical Care continues to invest extensively in research to find better ways to manage sepsis.

References
1. Eli Lilly and Company Data on file Source of data The Intensive Care National Audit & Research Centre 2. Natanson C et al Crit Care Med 1998,26 1927–31
† throughout England, Wales and Northern Ireland, ‡ defined as sepsis associated with acute organ dysfunction § these figures do not include cases of severe sepsis that occur either on wards or after the first 24 hours in the ICU

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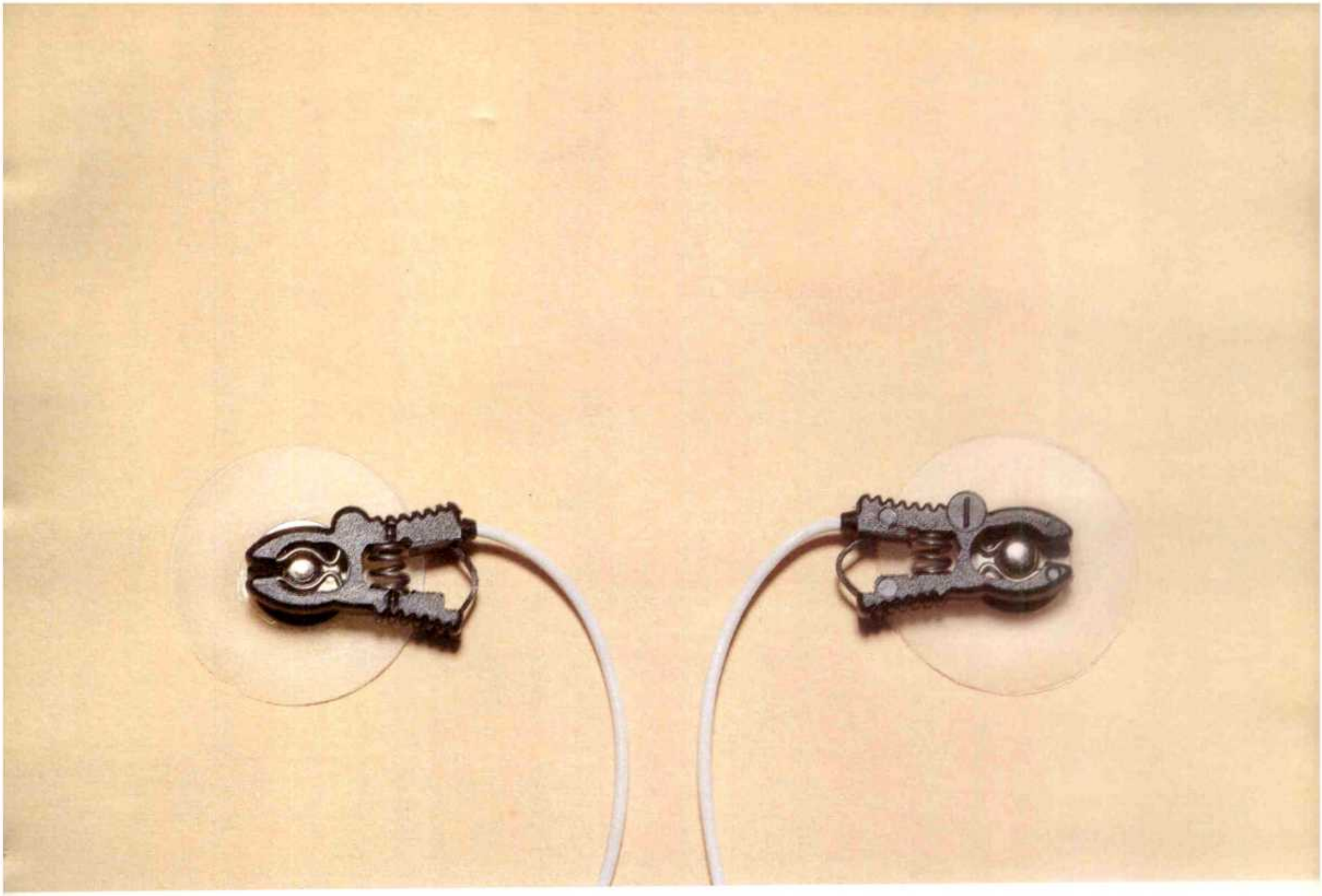

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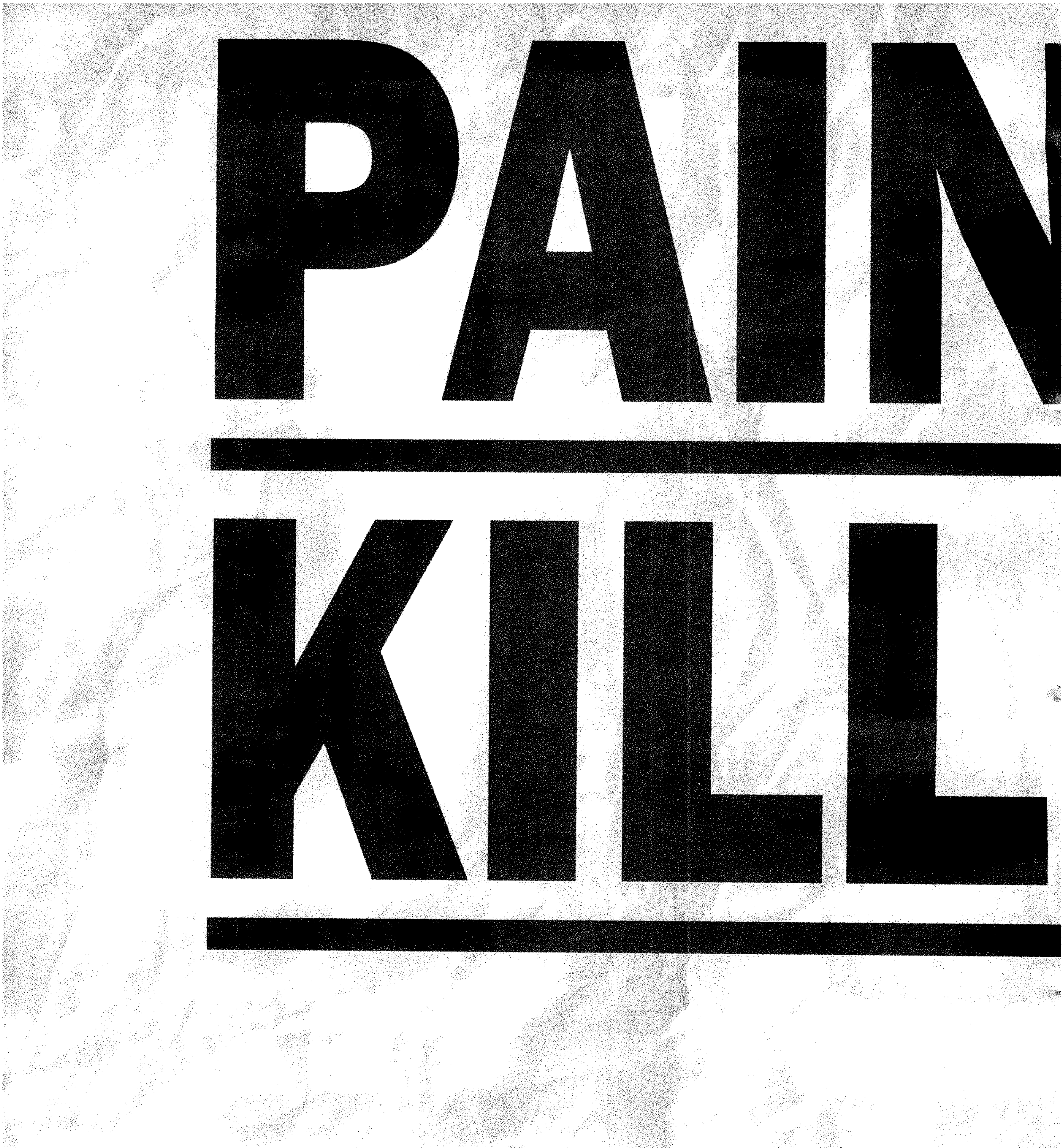

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Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib. Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension. Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib. Rofecoxib may mask fever. Use of rofecoxib is not recommended in women attempting to conceive. In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB. At chronic daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased. Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib. Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated. *Interactions (pharmacodynamic): Warfarin:* closely monitor the prothrombin time INR when therapy with rofecoxib is initiated or changed in patients receiving warfarin or similar agents, particularly
first few days. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril,
to 40 mg daily for four weeks to patients with hypertension was associated with a small atten
of the antihypertensive effect compared to the ACE inhibitor alone. This should be conside
patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* conco
use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the
effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once daily had no effect on th
platelet activity of low-dose (81 mg once daily) aspirin. Avoid concomitant administration of rof
with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal functio
rofecoxib and either cyclosporin or tacrolimus is used in combination. *Interactions (pharmacoki*
Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider ade
monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are admini
concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxi
drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zile
Midazolam: a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg
most likely due to increased first pass metabolism through induction of intestinal CYP3A4 ac
by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activi
pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affecte
clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4

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ib. *Rifampicin:* co-administration of rofecoxib with rifampicin, a potent inducer of CYP
s, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore,
r the highest dose when rofecoxib is used with potent inducers of hepatic metabolism. Based
tro data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.
ncy: Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis
rs rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib
not be used during the first two trimesters of pregnancy unless the benefit to the patient
ghs the risk to the foetus. *Lactation:* contra-indicated.

FFECTS

lowing drug-related undesirable effects were reported at an incidence greater than 1% and
than placebo in analgesia clinical studies in patients treated with rofecoxib 50 mg or 25 mg
5 days: dizziness, diarrhoea, diaphoresis, dyspepsia. The following drug-related undesirable
were reported at an incidence greater than placebo in osteoarthritis clinical studies in patients
with rofecoxib 12.5 mg or 25 mg for up to six months, or in post-marketing experience.
ion (≥1/100, <1/10); Uncommon (≥1/1000, <1/100); Rare (≥1/10,000, <1/1000); Very
1/10,000) and isolated cases]

s a whole/site unspecified: *Common:* oedema/fluid retention, abdominal pain, dizziness.
mon: asthenia/fatigue, abdominal distension, chest pain. *Very rare:* hypersensitivity reactions,
ng angioedema, urticaria and anaphylactic/ anaphylactoid reactions. ***Blood and the lymphatic system disorders:*** *Common:* haematocrit decreased. *Uncommon:* haemoglobin decreased, erythrocytes decreased, leukocytes decreased. *Very rare:* thrombocytopenia. ***Cardiovascular system:*** *Common:* hypertension. *Very rare:* congestive heart failure. ***Digestive system:*** *Common:* heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia. *Uncommon:* constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux. *Rare:* peptic ulcers, gastro-intestinal perforation and bleeding (mainly in elderly patients), gastritis. ***Hepatobiliary disorders:*** *Common:* alanine aminotransferase increased, aspartate aminotransferase increased. *Uncommon:* alkaline phosphatase increased. *Isolated cases:* hepatotoxicity including hepatitis and jaundice. ***Eyes, ears, nose and throat:*** *Uncommon:* tinnitus. *Very rare:* blurred vision. ***Metabolism and nutrition:*** *Uncommon:* weight gain. ***Musculoskeletal:*** *Uncommon:* muscular cramp. ***Nervous system:*** *Common:* headache. *Uncommon:* insomnia, somnolence, vertigo. *Very rare:* paraesthesia. *Isolated cases:* aseptic meningitis. ***Psychiatric disorder:*** *Uncommon:* depression, mental acuity decreased. *Very rare:* confusion, hallucinations. ***Respiratory system:*** *Uncommon:* dyspnoea. *Very rare:* bronchospasm. ***Urogenital:*** *Uncommon:* BUN increased, serum creatinine increased, proteinuria. *Very rare:* renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy. ***Skin and skin appendages:*** *Common:* pruritus. *Uncommon:* rash, atopic dermatitis. *Very rare:* alopecia. *Isolated cases:* cutaneo-mucosal adverse effects and severe skin reactions including Stevens-Johnson Syndrome. In clinical studies, the undesirable effects profile was similar in patients treated with rofecoxib for one year or longer. The following serious adverse effects have been reported in association with the use of NSAIDs and cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome; hepatotoxicity including hepatic failure.

PACKAGE QUANTITIES AND BASIC NHS COST

25 mg: packs of 14 tablets: £10.79. 50 mg: packs of 7 tablets: £5.39

Marketing Authorisation numbers: Tablet 25 mg PL 0025/0408. Tablet 50 mg PL 0025/0409

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POM **Date of review:** August 2001

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EPREX® ABBREVIATED PRESCRIBING INFORMATION

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use: increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM.

Product licence/authorisation holder:
Janssen-Cilag Ltd, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK.
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Date of preparation: February 2000

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*Haemoglobin levels >10 to ≤13 g/dL.

References:
1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz MC. *Orthopedics.* 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

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In moderately anaemic patients scheduled for orthopaedic surgery*

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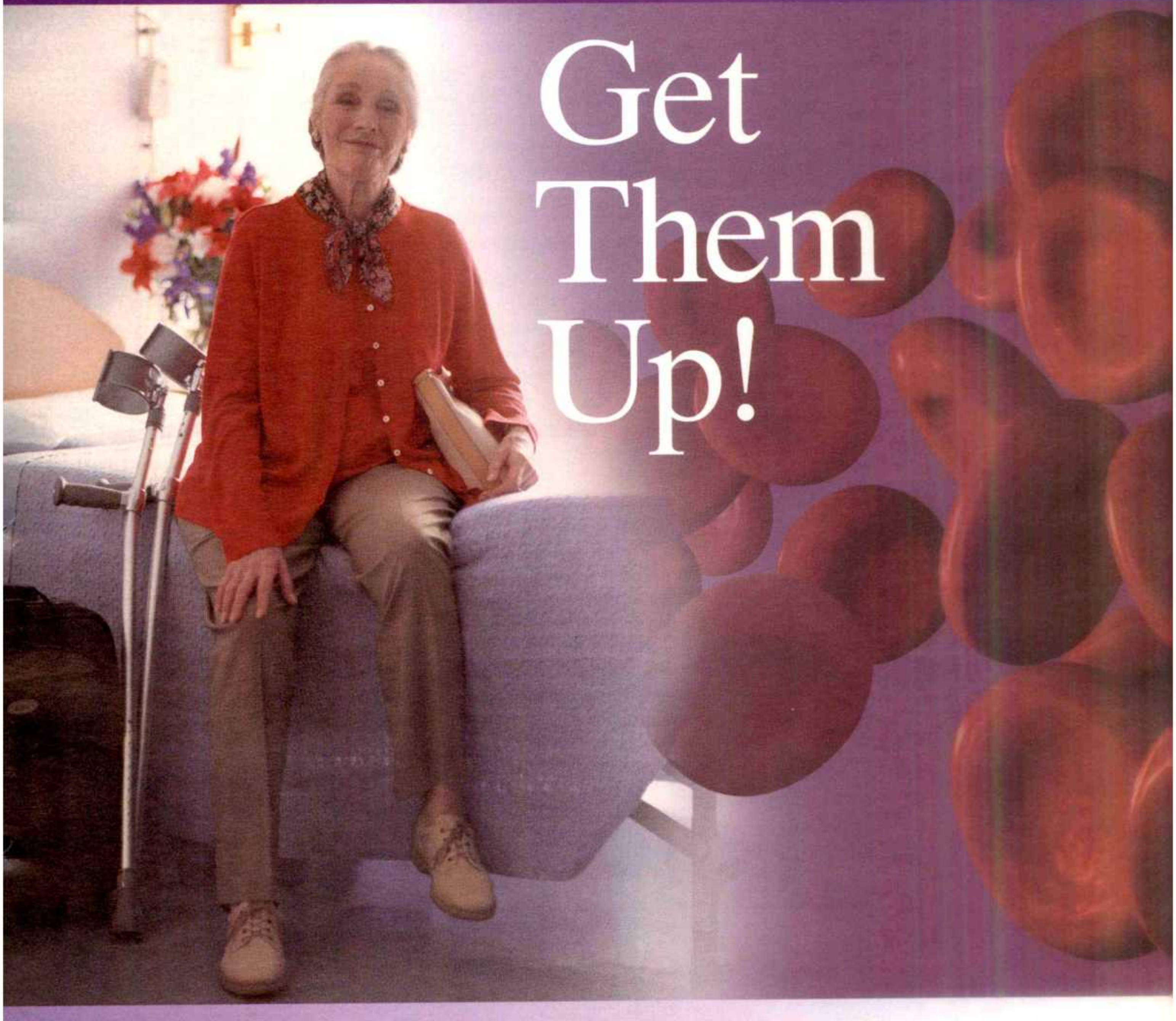

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Editorial Notices

STRUCTURED ABSTRACTS

From January 2002, the Summary of all Clinical Investigations, Laboratory Investigations and Short Communications (but not Reviews, Case Reports or Commentaries) published in the *British Journal of Anaesthesia* will be structured under the headings:

Background
Methods
Results
Conclusions

All new manuscripts submitted to the *British Journal of Anaesthesia* from 1 May, 2001 should therefore be presented in this format. If an Editor asks for a revised version of a previously submitted manuscript, please change the Summary in your next draft to the new structured format.

Jennifer M. Hunter
Editor-in-Chief

Royal Medical Benevolent Fund

President's Christmas Message for 2001

Readers of the *British Journal of Anaesthesia*, in recent years, have been generous in their response to my Christmas Appeal on behalf of the Royal Medical Benevolent Fund.

Those of us involved in the work of the Fund are constantly made aware of colleagues or their dependents whose lives have been torn asunder by unexpected tragedy. Throughout the year, the Fund provides support where it is needed. Last year, in financial terms, this amounted to a commitment of just over £1m.

It has become a tradition that at Christmas time we provide extra help—perhaps a gift, or more usually, a little more money; all the more welcome to buy presents when children are involved. Once again, though, we need your continuing kindness and generosity to enable us to give this additional seasonal cheer.

At this time last year we received over £73 000—a second record year. Please help once again in the hope that we can make Christmas for those less fortunate than ourselves approach their memory of happier times past.

Contributions marked 'Christmas Appeal' may be sent to the CEO of the RMBF, 24 King's Road, Wimbledon, London SW19 8QN or to the Treasurer of your local guild of this Fund. Thank You.

To those of you who have already contributed—thank you.

$500,000 IARS Frontiers in Anesthesia Research Award—Fourth Recipient

The Board of Trustees of the International Anesthesia Research Society (IARS) announced at the 75th Clinical and Scientific Congress the fourth recipient of the $500,000 IARS Frontiers in Anesthesia Research Award. The award was established by the IARS in 1994 'to foster innovation and creativity by an individual scientist in the field of Anesthesiology'. The fourth recipient is:
Mark A. Schumacher, PhD, MD, University of California, San Francisco, California.

Dr Schumacher's research project is titled 'Stretch-Inactivated Channels in Pain Transduction'. Dr Schumacher is an Assistant Professor in the Department of Anesthesia and Perioperative Care at the School of Medicine, University of California, San Francisco.

Primary FRCA Revision Course

Leicester Royal Infirmary, Leicester, UK, December 3–5, 2001

An intensive revision course for the Primary FRCA based on small group tutorials and including written and oral examination practice. Fees: £245 (including lunch and refreshments); £270 for two nights residential; £280 for three nights residential (limited availability). Course directors are Dr Justiaan Swanevelder and Dr Jonathan Thompson. Places are strictly limited.

For a booking form, please contact Christine Gethins on +44 (0) 116 258 5291 (anae@le.ac.uk).

7th Postgraduate Refresher Course: Cardiovascular and Respiratory Physiology Applied to Intensive Care Medicine

Free University of Brussels Campus Erasme, Brussels, Belgium, December 4–6, 2001

For further details, please contact: Mrs Veronique De Vlaeminck, Promotion des Soins Intensifs, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 2 555 32 15/36 31; Fax: +32 2 555 45 55; Email: sympicu@ulb.ac.be

International Scientific Meeting to celebrate the retirement of Professor R. S. Jones OBE, after 40 years in Veterinary Anaesthesia

The Racecourse, Chester, UK, December 6–7, 2001

Theme for the first day: 'Forty Years of Veterinary Anaesthesia'.

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European Society
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Nice
10th ESA Anniversary Meeting France
and 24th EAA Annual Meeting
Euroanaesthesia 2002

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Deadline abstracts:
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Online submission
www.euroanesthesia.org

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CENSA

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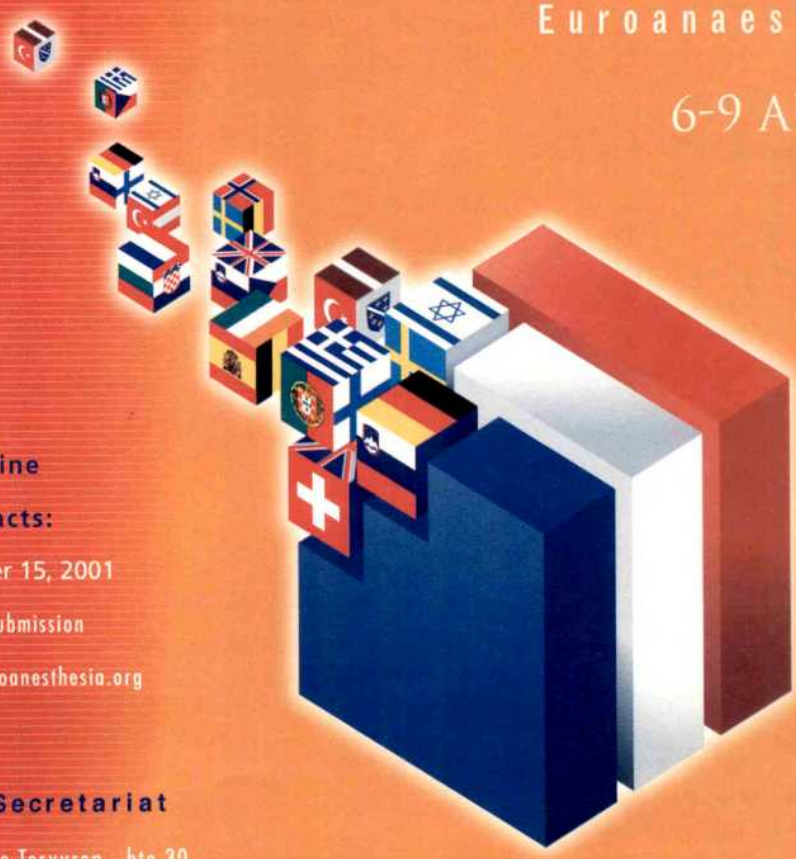

Theme for the second day: 'One Vet's Multidisciplinary Contributions'.

For further details please contact: Professor J. M. Hunter. Tel: +44 (0)151 706 4008; Fax: +44 (0)151 706 5884; E-mail: jwa@liv.ac.uk

3rd National Conference Indian Society of Neuroanaesthesiology and Critical Care (ISNACC-2002)

Mumbai, India, January 12–13, 2002

Venue: Choksi Auditorium, Tata Memorial Hospital, Parel, Mumbai.

For further details contact: Dr (Mrs) Kanchan S. Jagger, Room No. 423, 4th Floor, Department of Anaesthesia, L.T.M. Medical College Sion, Mumbai: 400022, India. Tel: +91 22 4022976 (O), +91 22 4371811 (R); Fax: +91 22 4076100; Email: kanchanjagger@yahoo.co.uk or isnacc2002@sify.com

20th Annual Symposium Clinical Update in Anaesthesiology and Advances in Techniques of Cardiopulmonary Bypass

Paradise Island, Bahamas, January 13–19, 2002

Abstract, Poster and Free Papers Information: (**Deadline – November 1, 2001**) Helen Phillips, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1010, New York, NY 10029-6574, USA. Tel: +1 212 241 7467; Fax: +1 212 426 2009; E-mail: helen.phillips@mssm.edu

Welcome to the second Euro-PNB winter symposium!

Postgraduate Course on Peripheral Nerve Blockade in Surgery and Pain Management for anaesthesiologists Excelsior Mila Hotel, Crans-Montana, Switzerland, January 16–19, 2002

Meet European experts in this stimulating course with workshops in an exciting environment.

Lecturers: Borgeat, Zürich, CH; J. Büttner, Mumau, DE; X. Capdevila, Montpellier, FRA; A. Ekblom, Stockholm, SE; E. Gaertner, Strasbourg, FRA; S. Gligorijevic, Zürich, CH; M. Jöhr, Luzern, CH; Z. Kosciclniak-Nielsen, Copenhagen, DK; D. Selander, Södertälje, SE; N. Suthcliffe, Glasgow, UK; T. Wildsmith, Dundee, UK.

Full participation certifies 15 Eu CME points. Fee: 250.-CHF. Places are limited to 40 delegates.

Registration before December 1, 2001 to: Assoc. Prof. Alain Borgeat, Head of Anaesthesia and Intensive Care, Orthopedic University Clinic, Balgrist/Zürich, Forchstrasse 340, CH-8008 Zürich, Switzerland.
Tel: +41 1 386 38 32; Fax: +41 1 386 16 09; E-mail: aborgeat@balgrist.unizh.ch

13th SW Thames Anaesthesia Update

Belle Plagne, French Alps, January 28–February 1, 2002

The scientific programme will include lectures and discussions on: Acute and Chronic Pain; Paediatric Update; Obstetric Anaesthesia; Neurology and Anaesthesia; ITU and Relevant Medical Topics; Cardiothoracic Anaesthesia; Day Case Surgery; Regional Blocks; New Drugs Update; Training and Education; Information Technology; Free Papers. Case Presentation Competition. Guest Speakers, Workshops, Videos on new Drugs, Equipment and Techniques.

Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: December 10, 2001. Meeting approved for CEPD.

For full information and to secure a place please contact: Dr J. B. Liban, Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT. Tel: +44 (0) 208725 0018; Fax: +44 (0) 208725 3135; E-mail: liban@mailbox. co.uk; Website: www.anaesthesiaupdates.com

10th Winter Symposium on Intensive Care Medicine

Crans Montana, Switzerland, February 3–8, 2002

For further details, please contact: Mrs Veronique De Vlaeminck, Department of Intensive Care – Symposium, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 2 555 47 57; Fax: +32 2 555 45 55; Email: sympicu@ulb.ac.be

Legal and Ethical Issues in Anaesthesia and Critical Care

Clinical Education Centre, Glenfield Hospital, Leicester, February 22, 2002

For further information please contact: Conference Co-ordinator, Clinical Education Centre, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK. Tel: +44 (0)116 250 2305; Fax: +44 (0)116 256 3334; Email: jackie.howarth@uhl-tr.nhs.uk

International Anaesthesia Research Society Annual Clinical and Scientific Congresses

March 16–20, 2002

IARS 76th Clinical and Scientific Congress, San Diego Marriott Hotel & Marina, San Diego, California, USA.

March 22–26, 2003

IARS 77th Clinical and Scientific Congress, New Orleans Marriott, New Orleans, Louisiana, USA.

March 27–31, 2004

IARS 78th Clinical and Scientific Congress, Tampa Marriott Waterside Hotel, Tampa, Florida, USA.

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Contra-indications: Allergy, hypersensitivity, peptic ulceration, severe renal impairment, pregnancy or lactation. **Warnings and precautions:** Mild-moderate renal impairment, liver disease, coagulation disorders, hypertension or obesity, long term treatment (>3 months), elderly patients. Monitor renal function in patients undergoing major surgery, with stressed renal function, cardiac failure, on diuretics or taking concomitant treatment suspected of causing renal damage. **Undesirable effects:** Frequency 1-10%. Tablets: Abdominal pain, diarrhoea, dizziness, dyspepsia, headache, nausea and vomiting. Injection: Abdominal pain, dizziness, fatigue, headache, injection site reactions, nausea, somnolence. See SPCs for details of adverse reactions occurring with frequency of less than 1%. **Legal categories, marketing authorisation numbers, package quantities and prices:** Xefo 8mg Powder for Injection: POM. PL 18467/0008. 1 vial - £2.25. Xefo 8mg Tablets: POM. PL 18467/0007. 30 tablets - £8.85. Xefo 4mg Tablets: POM. PL 18467/0006. 30 tablets - £8.85. **Marketing authorisation holder:** CeNeS Limited, Compass House, Vision Park, Chivers Way, Histon, Cambridge CB4 9ZR. Date of preparation: July 2001. **References:** 1. Norholt SE, *et al. Pain* 1996; **67**: 335-343. 2. Ilias W, Jansen M. *Br J Clin Pract* 1996; **50** (4): 197-202. 3. Rosenow DE, van Krieken F, Stolke D, Kursten FW. *Clin Drug Invest* 1996; **11** (1): 11-19. 4. Kidd B, Frenzel W. *J Rheum* 1996; **23** (9): 1605-1611. 5. Comprehensive evaluation of safety data in patients treated with lornoxicam. Data on file 1995. Eagle image © Dorling Kindersley.

XHJA001 July 2001

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March 11–15, 2005
IARS 79th Clinical and Scientific Congress, Hilton Hawaiian Village, Honolulu, Hawaii, USA.

Contact information: IARS, 2 Summit Park Drive, Suite 140, Cleveland, OH 44131, USA. Tel: +1 216 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Web: www.iars.org

22nd International Symposium on Intensive Care and Emergency Medicine

Congress Center, Brussels, Belgium, March 19–22, 2002
For further details, please contact: Mrs Veronique de Vlaeminck, Department of Intensive Care, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 2 555 32 15/36 31; Fax: +32 2 555 45 55; Email: Veronique.De.Vlaeminck@ulb.ac.be Website: http://www/intensive.org

Putting New Flesh on Old Bones: a major conference on Issues in the Perioperative Care of Geriatric Trauma

The Netherwood Hotel, Grange-Over-Sands, UK, May 10, 2002
Speakers include: Nigel Sharrock (New York); Martyn Parker (Peterborough)

Deadline for free paper abstracts: February 1, 2002.

Please contact Dr Andrew Severn for details: Tel: +44 (0)1524 583517; Fax: +44 (0)1524 583519.

Australian and New Zealand College of Anaesthetists Annual Meeting

Brisbane Convention and Exhibition Centre, Brisbane, Australia, May 11–15, 2002

For further information please contact:

ANZCA 2002 Secretariat, PO Box 1280, Milton QLD 4064, Australia.

Tel: +61 (0) 7 3858 5537; Fax: +61 (0) 7 3858 5510; E-mail: anzca2002@im.com.au; Website: www.anzca.edu.au

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Anaesthesia outside the square: CECANZ Conference 2002

Christchurch, New Zealand, September 18–20, 2002
For information, please contact: Conference Secretariat Joy Mehlhopt, Conference Innovators, P.O. Box 1370, Christchurch, New Zealand.

Tel: +61 3 379 0390; Fax: +61 3 379 0460; E-mail: joy@conference.co.nz. Website: www.cecanz2002.org.nz

Société Française d'Anesthésie et de Réanimation

Annual congresses will take place in Palais des Congrés, Porte Maillot, Paris on the following dates:

September 26–29, 2002
September 18–21, 2003
September 20–October 3, 2004
September 29–October 2, 2005

For further information, please contact: SFAR, 74, rue Raynouard, F-75016 Paris, France. Tel: +33 1 45 25 82 25; Fax: +33 1 40 50 35 22; E-mail SFAR@invivo.edu

Dingle 2002—4th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 2–6, 2002
For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

Australian Society of Anaesthetists National Scientific Congress

Adelaide, Australia, October 26–30, 2002
This is the Society's premier scientific conference, held in an interesting part of the world.

For further details, please contact: Festival City Conventions, P.O. Box 949, Kent Town, S.A. 5071, Australia. Tel: +61 (0)8 8363 1307; Fax: +61 (0)8 8363 1604: E-mail: asa2002@fccconventions.com.au

8th International Congress of Cardiothoracic and Vascular Anesthesia
19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002
For further information regarding the Congress, please contact:

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Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H.Rosenberg, Helsinki University Hospital, Helsinki FIN00029 HUS, Finland.

E-mail: per.rosenberg@hus.fi
Or: CONGREX/Blue & White Conferences Oy

E-mail: congrex@congrex.fi
Web address: www.congrex.fi

Dingle 2003—5th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 1–5, 2003

For further information contact:

Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

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AMBULATORY ANESTHESIA (Society for Ambulatory Anesthesia)

1373 Local Anesthesia for Hernia Repair
1377 Ambulatory Selective Spinal Anesthesia (Brief Report)

PEDIATRIC ANESTHESIA (Society for Pediatric Anesthesia)

1380 Remifentanil Anesthesia in Infants
1387 Remifentanil and Pneumocardiograms in Infants
1393 Pharmacokinetics of Remifentanil in Children

CARDIOVASCULAR ANESTHESIA (Society of Cardiovascular Anesthesiologists)

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1501 Effect of Lidocaine on p47 Phox Translocation in Neutrophils
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1511 Long-Duration Low-Flow Anesthesia
1521 Pentobarbital and Synaptic Hippocampal Transmission
1526 Esmolol Promotes EEG Burst Suppression
1532 Remifentanil and Seizure Activity (Case Report)

TECHNOLOGY, COMPUTING, AND SIMULATION (Society for Technology in Anesthesia)

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ECONOMICS AND HEALTH SYSTEMS RESEARCH

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1565 Early Pregnancy and Propofol
1570 Hemodynamics in Pregnancy Laparoscopy (Case Report)

PAIN MEDICINE

1572 Chronic Melanocortin-Receptor Blockade and Neuropathic Pain
1578 Body Temperature and Diaphoresis Disturbances (Case Report)

REGIONAL ANESTHESIA

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Editorial I

Central noradrenergic neurones and the mechanism of general anaesthesia

Modern anaesthetics are, in the main, safe and predictable in their use, and highly efficient. Moreover, it could be argued that without these properties major advances in surgical practice, so often highlighted in the media, could not have taken place. However, as an example of pharmacology, the production of the anaesthetic state remains somewhat of a mystery. This mystery results from the controversies related to the existence of a unitary anaesthetic target site. From direct observation of clinical anaesthesia, this seems unlikely as different anaesthetic agents produce different 'types' of anaesthesia. $GABA_A$ receptors have long been held as a unifying cellular target (with some exceptions), but others have also been suggested. In this editorial, we consider the evidence in support of a role for noradrenergic transmission as a 'wiring' target for anaesthetic action. The clear role of this system in analgesia is not considered.

Norepinephrine is a major central nervous system neurotransmitter in the brainstem. Noradrenergic neurones are of great importance in the regulation of a range of behaviours including the sleep–wake cycle, feeding, thermoregulation, attention, motor activity, and growth and development.[1] In addition, there are many studies suggesting that noradrenergic system(s) may be involved in the production of the 'anaesthetic state'. In the brain, the A1, A2, A5, and A7 noradrenergic clusters constituting the lateral tegmental area, project to the thalamus and hypothalamus.[2] The locus coeruleus (A6 cluster), which is distinct from the lateral tegmental area, innervates the cerebral cortex, hippocampus, cerebellum, and spinal cord.[2]

The activity of locus coeruleus neurones is slow and regular during wakefulness.[3] In contrast, when an animal becomes drowsy, entering slow wave and then REM sleep, there is a decrease in discharge rate such that during REM sleep these neurones are silent.[3] Interestingly, all noradrenergic projections to the cerebrocortex originate from the locus coeruleus.[3]

The preoptic area receives input from both the locus coeruleus (A6), and the lateral tegmental group (A1, A2, A5, and A7) noradrenergic neurones.[4] In addition, neurones in the preoptic area project back to the locus coeruleus.[5] This area plays an important role in sleep or hypnosis. What is the role of noradrenergic neurones in this area? Most of the previous studies[6] suggest that norepinephrine neurones in the preoptic area may contribute to wakefulness, as direct activation or injection of norepinephrine into this area inhibits sleep. However, several studies also suggest that some norepinephrine neurones may be involved in the induction of sleep.[7 8] Mohan Kumar and colleagues[7] reported that microinjection of norepinephrine into the medial preoptic area after destruction of the ventral noradrenergic bundle induced sleep. This group also reported that there was a mild reduction in sleep and an increase in wakefulness after destruction of catecholaminergic terminals at the medial preoptic area by bilateral intracerebral injection of 6-hydroxydopamine.[8] Thus, it appears that noradrenergic fibres in the medial preoptic area may be hypnogenic.

Central noradrenergic neurones are regulated by both α- and β-adrenergic receptors. It has been reported that the α_1-adrenoceptor antagonist prazosin, given orally, increased active waking and slow wave sleep and decreased paradoxical sleep in the rat.[9] In contrast, α_1-adrenoceptor stimulation with systemic methoxamine, increased aroused wakefulness and decreased slow wave sleep and paradoxical sleep in cats.[10] In addition, prazosin increased but the α_1-agonist ST 587 decreased the duration of thiopental anaesthesia in rats.[11] Matsumoto and colleagues also reported that direct intracerebroventricular administration of methoxamine dose-dependently reduced pentobarbital anaesthesia time in mice[12] Most of the central physiological effects of α_2-agonists can be attributed to α_2-adrenoceptors present in the locus coeruleus.[13] In rats, microinjection of the α_2-agonist dexmedetomedine into the locus coeruleus *per se* produces anaesthesia (defined as a loss of righting reflex).[14] α_2-Agonists also reduce anaesthetic requirement in human and many other species.[15] In contrast to these data, the α_2-antagonist yohimbine decreases sleep,[16] and anaesthesia time[15] in a variety of non-human species.

The Angel group showed that propranolol, a non-selective β-antagonist, dose-dependently increased sleep time[16] and thiopental anaesthesia time[11] in rats. However, they failed to show an effect with the selective β_1-antagonists metoprolol and atenolol.[11 17] They also studied the role of β_2-adrenoceptors in sleep and general anaesthesia,[11 16 17] and found that the selective β_2-antagonist ICI

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118551 increased sleep time[16] and the duration of thiopental anaesthesia.[17] Collectively, these data indicate that the effects of the non-selective antagonist, propranolol, may be mediated via β_2-adrenoceptors.

The recently identified (from rat hypothalamus) neuropeptides orexin A and B[18] are endogenous agonists for the G-protein-coupled orexin-1 (OX1) and OX2 receptors.[18] Orexin A has equal affinity for OX1 and OX2, while orexin B has a higher affinity for OX2. Orexins and their receptors are widely distributed in the brain.[18] Orexins activate the locus coeruleus noradrenergic system and this activation may increase arousal and locomotor activity.[19] In addition, several reports[20] suggest a link between orexin receptors and narcolepsy. Therefore, modulation of noradrenergic neurones by orexins and their receptors may contribute to control of the sleep–wake cycle. Moreover, we suggest that these neuropeptides and their receptors may also be involved in general anaesthesia, although this remains to be examined.

Based on these considerations, we and others have began a systematic evaluation of a range of anaesthetic agents on central norepinephrine release using *in vivo* microdialysis techniques. Mizuno and colleagues reported that intraperitoneal pentobarbital inhibited norepinephrine release from the medial preoptic area in rats.[4] In addition, we have shown that systemic administration of midazolam and propofol significantly reduced norepinephrine release from the medial prefrontal cortex,[21] but pentobarbital was ineffective.[22] As noradrenergic neurones in the prefrontal cortex receive innervation from the locus coeruleus,[3] the activity of noradrenergic neurones in the prefrontal cortex indirectly reflects locus coeruleus activity. Thus, anaesthetics that activate or enhance $GABA_A$ receptors may reduce noradrenergic neuronal activity. In contrast, ketamine,[21 22] nitrous oxide and xenon,[23] which have NMDA receptor antagonistic actions, markedly increased norepinephrine release from the prefrontal cortex and preoptic area in rats. Clearly, anaesthetic modulation of norepinephrine release depends on the type of anaesthetic. This might argue against noradrenergic transmission as an anaesthetic target. However, as we have already mentioned, a unitary site is highly unlikely. Loss of consciousness results not only from a reduction in cerebral activity, but also as a result of cerebral excitation such as occurs during convulsions. In addition, sleepiness is induced by not only hypothermia but also by increased body temperature that activates heat-sensitive neurones in the preoptic area.[24] We feel that wakefulness may occur over a set range and that when this range is exceeded (above *or* below), unconsciousness may occur. In support of this hypothesis we found that physostigmine, which has been reported to antagonize ketamine anaesthesia, reduced both the duration of ketamine anaesthesia and ketamine-increased norepinephrine release from the rat prefrontal cortex.[25]

Collectively, the data presented in this editorial provide compelling evidence in favour of a role for noradrenergic transmission in both the control of wakefulness and the production of the 'mysterious' anaesthetic state.

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Editorial II

Comparative mortality in anaesthesia

Ever since the advent of general anaesthesia in 1846, the subject of anaesthetic mortality has been a source of considerable debate and discussion. In the late 1880s, the Hyderabad Commissions concluded that chloroform was a completely safe anaesthetic agent in the human species.[1] The *Lancet* commissioned its own study and this was probably the first epidemiological investigation of the effects of anaesthetic agents in any species.[2] On the basis of animal experiments, the Hyderabad Commissions had concluded that chloroform was a safe agent in man but the *Lancet* Commission challenged these findings. They concluded that death under chloroform anaesthesia was 8.7 times more likely than death under ether anaesthesia, whereas chloroform was only administered 6.1 times more often than ether. Whilst the members of the commission failed to establish the relative safety of ether or chloroform, they focused attention on the role of human error in the aetiology of anaesthetic deaths. It took the greater part of 50 yr before the real problems of anaesthetic deaths and their prevention became the subject of intense study by a number of anaesthetists throughout the world. It was only during that time that the real value of properly maintained anaesthetic records was emphasized by Waters.[3] However, it was not until 1954 that a well-designed and executed survey was reported by Beecher and Todd.[4] They collected data on 600 000 patients from 10 university hospitals over a 5-yr period. The report caused considerable controversy, in that it reported a considerably higher mortality in patients that had received the newly introduced muscle relaxant drugs compared with those that did not.

One of the major problems in surveys of anaesthetic mortality is its actual definition and how this relates to surgical and overall mortality; these problems have been discussed by Duberman and Bendixen.[5] With the refinement of both anaesthetic and surgical techniques, patients with extensive pathology are being anaesthetized who in a previous era would not have undergone surgery. Hence, it is extremely difficult to compare anaesthetic mortality on a historical basis.

In 1973, following a computer analysis of deaths associated with anaesthesia, Marx and his colleagues reported that the mortality within the first 7 days of surgery was 1.9%.[6] They considered that two main factors determined the mortality rate—the physical status of the patient and the skill and judgement of the physicians. Two-thirds of the deaths were considered to be preventable. In a further survey from Australia in 1975, Bodlander showed that the incidence of deaths associated with anaesthesia was one in 502 (0.2%).[7] The number of deaths attributable to anaesthesia showed a marked fall from 20% to 3.7% of the total mortality over the 10-yr period of the survey. The definitive work on anaesthetic mortality in the UK has been published by Lunn and Mushin.[8] They reported that one in 166 (0.6%) of patients died within 6 days of surgery but only one in 10 000 deaths (0.01%) is directly attributable to anaesthesia. They went on to report that, in a much larger number of 1800 deaths, anaesthesia may play some part in one in 1700 (0.06%), and they suggested that this could, in large measure, be avoided. The events that caused these deaths do not appear to have changed over the past 30 yr.

In a study of 7306 patients in Denmark by Pedersen and colleagues in 1990, it was reported that one in 1800 (approximately 0.05%) died during anaesthesia, one in 730 (>0.1%) during the recovery period, and the overall hospital

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mortality rate was one in 81 (1.2%).[9] In an assessment of anaesthetic mortality, Keats suggested that 'anesthesia mortality has not decreased because we create new mechanisms of mortality at the same rate as we solve them'.[10]

In veterinary anaesthetic practice, it is extremely difficult to collect meaningful statistics on the subject of anaesthetic mortality, due to the diverse nature of veterinary practice and the absence of a Coroner's Court system. Hence, there is no real need or incentive to record or report anaesthetic deaths. However, on the basis of scientific curiosity, a number of surveys have been reported and, overall, there is a greater interest in the subject over the past 10 yr.

Horses

Anaesthetic mortality in horses has always been considered to be relatively high compared with most other species and has been attributed to the size and bulk of the horse, and to its unique cardiopulmonary physiology as a highly evolved athletic animal. However, in a series of some 600 horses which had received chloral hydrate by the i.v. route, Wright and Hall reported only two deaths (0.3%).[11] With the development of extensive gastrointestinal surgery in the horse, the mortality rate has risen and a rate of 1.18% has been recorded more recently. [12] It is important to separate the animals undergoing *elective* surgery from those undergoing *emergency* abdominal surgery, which have extensive abdominal pathology, and are extremely hypovolaemic and in endotoxic shock. Resuscitation of these animals presents a massive challenge. In a series of horses reported in 1983 from Norway, a mortality of 33 in 1216 (2.7%) was reported but anaesthesia was responsible for only 0.8%.[13] In a further study of 1314 equine general anaesthetics reported from a single centre in 1993 by Young and Taylor, the mortality was 0.68%.[14] The main causes of death were ischaemic myopathy (which is similar to compartment syndrome), fracture of the cervical or long bones, and cardiac arrest. It was not until 1995 that accepted epidemiological principles were applied to anaesthetic mortality in horses. A confidential enquiry by Johnston and colleagues surveyed a total of 6255 equine general anaesthetics and reported an overall mortality of 1.6%.[15] When abdominal surgery and foals were excluded, the rate fell to 0.9%. They identified a number of factors, which led to a higher mortality, including anaesthesia in the third trimester of pregnancy, emergency abdominal surgery, orthopaedic procedures involving internal fixation, and the administration of xylazine. Xylazine is a relatively non-specific alpha$_2$-adrenoreceptor agonist, which was the first one of that group of drugs to be used in domestic animals. It has similar cardiovascular effects to the other drugs in that group, but the actual cause of death after xylazine is uncertain. The risk of death also increased with the duration of anaesthesia, when it was carried out outside normal working hours, and in foals under 1 yr old. In a further single centre study, Mee and colleagues reported on a series of 2276 horses undergoing *elective* surgery under general anaesthesia.[16] A death rate of 0.63% was attributable to surgery/anaesthesia but the rate for anaesthesia was only 0.08%. The cause of death in the one horse was cardiac arrest 15 min after induction of anaesthesia in which resuscitation was unsuccessful. Post-mortem examination failed to establish a cause of death. In contrast, in a further series of 995 horses undergoing *emergency* procedures, the same authors reported a mortality of 31.4%.[17] In abdominal surgery, the gross mortality was 35.5% and in the non-abdominal surgery group it was 15.3%. The surgical/anaesthesia death rate was 4.3% in the abdominal surgical group and 2% in the other group. The main causes of death were cardiac arrest, uncontrollable massive haemorrhage, and irreversible endotoxic shock. In a later report in 2000, Johnston and his colleagues reported on 41 787 equine anaesthetics.[18] The overall death rate was 1.9%. When abdominal surgery was excluded, the rate was 0.9% but, for abdominal surgery, it was 7.9%. The most common causes of death were cardiac arrest (33%), fractures (23%), and ischaemic myopathy (7%).

Small animals

In cats and dogs, there is a little more information available from surveys conducted over the past 50 yr, although the main information has been published in the past decade. A survey of 2912 anaesthetics administered in one institution, between 1955 and 1957, recorded a mortality of 1.1% in dogs and 1.8% in cats.[12] A follow-up survey in 1979–1981 showed a reduction to 0.43% in dogs and 0.25% in cats. The main cause of death was attributed to human error leading to anaesthetic overdosage and to hypoxia. Equipment problems, hypothermia, and cardiovascular collapse were other causes of death. A survey of 10 000 feline anaesthetics in Scotland reported a death rate of 0.3%.[19] The main causes of death appeared to be related to the failure to obtain accurate body weights of the animals, to use adequate and effective pre-medication, and to intubate the trachea.

In 1990, a survey of 20 814 dogs and 20 103 cats undergoing general anaesthesia in the UK reported a mortality of 0.23% in dogs and 0.29% in cats.[20] However, when they were divided into two groups, on the basis of the absence or presence of pathology, a different situation was observed. In dogs, the figure was 3.12% with pathology and 0.11% without. In cats, a similar pattern was observed with a mortality of 3.33% with pathology and 0.29% without. There were few factors that could be highlighted as the main cause of death. However, the administration of xylazine was again associated with an exceptionally high mortality rate. Complications following tracheal intubation in the cats appeared to be associated with several deaths.

In a survey involving some 30 000 anaesthetics reported in 1992, a mortality rate of 0.11% was reported in dogs and 0.06% in cats.[21] The most common cause of death was cardiopulmonary arrest. A further single institution survey published in 1994 recorded a death rate of 0.43% in dogs and cats.[22] Most of the deaths were associated with cardiac arrest and, due to the nature of the surgical condition, resuscitation was not attempted in some of these animals. A more recent survey was published in 1998 on anaesthesia in the dog and cat.[23] Death occurred in 0.11% of 8087 dogs and in 0.1% of 8702 cats. Significant odds ratios were calculated for a number of factors including the association of cardiac arrest with xylazine administration in dogs. A modified ASA classification of patient status was adopted, and a classification of 3, 4, or 5 was also associated with an increased incidence of cardiac arrest in both species.

It would appear that the incidence of death associated with anaesthesia over a number of years has shown a reduction in most species. Whilst this may well have been associated with the development of 'safer anaesthetic techniques', it is most likely also to have been associated with attempts to reduce human error by improved training and wider use of sophisticated monitoring methods. However, with the developments in surgery, which have presented greater challenges to the anaesthetist, it remains to be seen whether further major improvements in mortality figures will occur in the foreseeable future.

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Editorial III

PCA: patient-controlled analgesia or politically correct analgesia?

Patient control: distinguishing reality from rhetoric

Politicians, managers, and clinicians have written and spoken a great deal in recent years about patient involvement and choice in health care. The word 'patient' has even given way in some contexts to 'user' or 'customer', as consumer-orientation has displaced the traditional view of the patient as a passive recipient of experts' care. Although it is the rhetoric of health care that has changed most

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obviously, there have been some tangible changes in patient management that emphasize patients' active role. The rapid and widespread adoption of patient-controlled analgesia (PCA) as a method of acute pain management should be understood in this context.

For PCA to be accurately described as patient-controlled analgesia, both patients and staff have to change their attitudes and behaviour. Patients, instead of relying on anaesthetists to prescribe analgesia and on nurses to administer it, have to feel able to take control of their analgesia and then to exercise control. We have examined in detail patients' perspective on PCA to find out whether they adopt this role.[1–4] Unfortunately, concerns about overdosing and side effects, mistrust of technology, and ambivalent attitudes to the need to feel, or avoid, pain all restricted patients' freedom to control pain by using PCA. Even patients who said that they had 'complete control' over their pain still had side effects, felt that PCA was unsafe or that the machine did not always work correctly.[3] Although PCA is popular with patients,[1 5] this cannot be attributed to improved pain relief, because there is little advantage over nurse-administered analgesia,[5 6] and the evidence of patients' perspective has failed to support the notion that PCA is popular because it affords patients control. On the contrary, we found that patients liked PCA because it freed them from the need to exercise control by 'bothering' nurses with their requests for analgesia.

The results of intensive investigation of the patients' perspective are, therefore, inconsistent with the rhetoric surrounding PCA. Patients do not, in general, embrace the opportunity for control over their pain relief. Their stance is probably not specific to PCA, or to technological approaches to empowerment: surgical patients also rejected a purely psychological attempt to encourage them to feel in control of their postoperative care and recovery.[7]

A new role for staff?

Just as PCA presents patients with a new role, it necessitates a corresponding change in the attitudes and behaviour of nurses and anaesthetists who have to accept that they are no longer in charge of pain relief and must devolve this to the patient. As a general statement this appears straightforward. However, when resolved into the specific changes that are needed, the enormity of the required reversal in the staff role becomes clearer. Most obviously, PCA requires staff to trust patients to make their own decisions about when they need analgesia and how much they need. It follows that staff will have to tolerate patients who seem to under-medicate themselves. For instance, they should respect the decisions of patients who prioritize avoiding side effects over gaining pain relief. Conversely, they should not harass patients who inject more analgesic than staff think that they need. Staff should trust patients to treat themselves wisely, reassured by the knowledge that PCA machines observe lock-out periods and maximum dosages. Staff should also respect patients' decisions to inject morphine to help them sleep, or to provide reassurance.

A further change in the staff role must follow from devolving pain-control to the patient. Staff—who remain responsible for other aspects of care—will have to negotiate with patients where their different responsibilities meet or potentially conflict. In this respect, the patient should be treated as another member of the clinical team—a difficult concept for many staff.

The role for staff that we have outlined contradicts the self-image of medical and nursing staff as the experts and it is incompatible with the entrenched paternalistic attitudes and behaviour of staff to patients. However, it is implausible to suppose that previous attitudes that 'staff know best' and that 'patients can't be trusted' have been reversed so effectively, particularly in the absence of any commensurate change in staff training and in the face of patients' continued deference to staff authority. Professions do not give up their power so easily.

Why, therefore, is PCA so popular with staff, judged by their attitudes to it,[8] and by the extent of its use? Certainly, it fits the rhetoric of patient empowerment, but this is hardly likely to matter to staff on the ward. A clue to a more likely explanation is the finding that *patients* value PCA because it avoids having to disclose their pain to staff or to 'bother' them.[2] The implication is that patients fear disapproval for doing either. There is, indeed, evidence that nurses at least, dislike or disapprove of patients who show that they are distressed or in pain.[9] Therefore, they distance themselves psychologically from them—for example, by regarding patients as complaining rather than suffering.[10] PCA might be valued by staff because it provides a novel way to distance themselves psychologically from patients in pain.

PCA achieves distancing because, whereas the rhetoric is about giving patients *control* of pain management, the reality is that it makes patients *responsible* for pain management. There is nothing novel in the suggestion that clinicians devise procedures for shifting responsibility from themselves to patients. In chronic pain management, this manoeuvre is well understood. Pain management programmes use cognitive–behavioural techniques to emphasize the patients' own role in modulating their pain and managing its effect on their lives. The function of these programmes is to transfer responsibility from staff to patients for a problem that staff are no longer willing, or able, to resolve.

The need for research into the staff perspective

Whereas our description of the patient perspective is based on published evidence, there is virtually no work on staff attitudes and behaviour. Our account of patients' perspective does, however, contain a clue that staff find it difficult to cede control: almost half of a sample of 200 patients reported that they pressed the PCA button when told to by nurses or others.[3] Systematic research into the staff perspective is now needed. Evidence that would test our argument would be whether or not, upon careful and detailed observation, staff routinely disapprove of patients' decisions about the use of PCA or try to influence them. It will not be difficult to gather the relevant evidence. Indeed, we can illustrate the kinds of evidence that would support our case from observations that we made in the course of a recent study of the management of postoperative pain in paediatric patients.[10] Reports by parents provided observations that, if replicated systematically, would indicate that staff control PCA. For instance, one mother explained that her daughter '*had been taken off her morphine because she has been pressing it too much. .. The nurses said she's overdosed*'. Another complained that '*the doctor came and told us that [child] was pressing the button too much before. .. She'll be taking too much*'. The same child also found that '*the night nurse told me off for pressing the button too much, but I wanted to press it because I was in pain, but she said I couldn't press it any more at all*'. Other descriptions of meddling by staff showed that patients experience contradictory attempts to control PCA. A father whose child was nauseated explained that '*the nurses thought it was the morphine so she stopped pressing the button. She was in really extreme pain for about 6 h*', but that later '*the anaesthetist came up and said it wasn't the morphine so she began pressing it again. She feels really sick all the time now though.*' Interestingly, nurses reported that some patients used PCA 'sensibly', but this meant sparingly; for example '*she's being much more sensible with her PCA. She's not pressing it as much as she was before*'. A critical difficulty with nursing and medical staff's concept of 'overuse' is that patients are unable to monitor their drug administration in the way that an objective professional could. As one parent explained, '*It must be really difficult for [child] to know how many times she has pressed it and everything. I mean she keeps falling asleep and waking up. How would she know?*'

It will also be possible to gather evidence to show whether staff respect the patient's right to negotiate with them as members of the care team. An observation from our study of paediatric pain management[10] illustrates the kind of finding that, if replicated systematically, would indicate that staff do not accept this right (we did not observe any evidence of patients successful negotiating with staff):

Nurse. *Shall we turn you?*
Patient. *Please come back in a few minutes, and then you can.*
Nurse. *That won't make any difference. .. come on, let's turn you over.*
Patient. *Please don't touch my scar. Please, please, why can't you come back in two minutes when the morphine has worked. Oh mum, mum.*

Towards a realistic understanding of PCA

The observations provided above only illustrate our argument, and they emerged in the course of research in which PCA was peripheral. Moreover, the patients were children, so adult–child power relationships might have contributed to staff reluctance to cede control or negotiate. Nevertheless the observations are consistent with our previous report that patients sometimes pressed the PCA button when instructed.[3] Unfortunately, we did not think to ask in that study whether patients sometimes *refrained* from pressing when told *not* to. Until the necessary studies are undertaken, there remains no evidence that traditional attitudes of staff surrounding pain-control have changed to accommodate the autonomous patient, and PCA cannot be regarded as patient-controlled.

The evidence that is already available suggests that patient control is a political and professional construction rather than a product of patients' own aspirations.[2 3 7] If research into the staff perspective mirrors what we know from the patient perspective—that control is neither devolved by staff nor embraced by patients—research should, therefore, go on to examine what drives the construction of patient empowerment of which PCA is an exemplar. We have proposed that the answer does not lie entirely in political correctness. The search should examine the influence of emotional factors that have long been known to degrade clinicians' relationships with patients, by helping them to distance themselves psychologically from patients and to evade feelings of responsibility for patients' pain and suffering. Clearly, in some situations, such as chronic intractable pain, it may be appropriate to transfer responsibility to patients whereas, in others, clinicians must retain responsibility. There is a need for a more realistic debate about the functions and effects of techniques such as PCA, that seek to empower patients, and for careful analysis to show when these techniques are genuinely in patients' interests. This debate must be grounded in empirical research into what staff and patients do, rather than in assumptions that merely recycle the tired rhetoric of patient empowerment.

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CLINICAL INVESTIGATIONS

Cardioventilatory coupling in heart rate variability: the value of standard analytical techniques

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In a group of spontaneously breathing anaesthetized subjects, we examined the ability of simple spectral and non-linear methods to detect the presence of cardioventilatory coupling in heart rate time series. Using the proportional Shannon entropy (H_{RI-I}) of the RI_{-I} interval (interval between inspiration and the preceding ECG R wave) as a measure of coupling, we found no correlation between H_{RI-I} and either the fractal dimension or approximate entropy of the heart rate time series. We also observed no difference in the distribution of heart rate variability (HRV) spectral power in three frequency ranges (high, 0.15–0.45 Hz; low, 0.08–0.15 Hz; very low, 0.02–0.08 Hz) between uncoupled epochs and coupling patterns I, III and IV. Because of its association with low breathing frequencies, pattern II coupling epochs showed exaggerated low-frequency power as the high-frequency 'respiratory' peak fell into the low-frequency range. We conclude that coupling pattern is largely independent of autonomic tone and that these standard methods of HRV analysis are limited in their ability to detect the presence of cardioventilatory coupling in heart rate time series.

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Beat-to-beat heart rate variability (HRV) is mediated primarily by variations in the level of sympathetic and parasympathetic modulation of the sinoatrial node. Certain methods of HRV analysis are therefore useful for examining cardiac autonomic tone.[1] Because different reflexes within the heart rate control system are active within different frequency ranges, frequency domain analysis of heart rate time series allows the relative contribution of each reflex pathway to be distinguished. Three component periodicities make up the typical heart rate time series. Fast periodicities in the range 0.15–0.45 Hz are largely due to the influence of respiratory phase on vagal tone [respiratory sinus arrhythmia (RSA)]. Low-frequency periodicities, in the region of 0.08–0.15 Hz, are produced by baroreflex feedback loops associated with sympathetic, activity and periodicities in the frequency range 0.02–0.08 Hz have been variously ascribed to modulation by chemoreception, thermoregulation and the influence of vasomotor activity.[2] These regions commonly overlap, as in the case of subjects breathing slowly at respiratory frequencies approaching 0.1 Hz.

In addition to frequency domain analysis, there has been considerable interest in the analysis of HRV using non-linear methods, such as the fractal dimension (D_F) and approximate entropy (ApEn), both of which attempt to quantify the complexity of heart rate dynamics.

The fractal dimension is a quantification of the space-filling propensity of the heart rate time series. While in Euclidean geometry a line is one-dimensional and a surface is two-dimensional, an irregular curve can be thought of as a line which is attempting to fill a surface. Mathematically, we can therefore describe such a line as having a dimension between one and two. The more the line fills the plane, the higher will be its fractal dimension D_F.[3]

Entropy is a quantification of the repetition of patterns within a given signal.[4] Small values of entropy are associated with regularity of patterns within a signal, such that it may be possible to predict the recurrence of a previously identified pattern. Larger values of entropy are associated with greater apparent randomness. Steven Pincus has developed a measure of entropy, 'approximate entropy' (ApEn), as a modification of

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Kolmogorov–Sinai entropy to allow measurements of entropy from shorter data segments, with simpler mathematics and lower computational demands.[5 6] ApEn has been applied to the study of HRV by a number of authors.[5 7 8]

Cardioventilatory coupling is a temporal coherence of cardiac rhythm and inspiratory timing.[9] It is seen in resting subjects, during sleep and spontaneous-breathing general anaesthesia. Experimental and clinical observations are consistent with coupling being a triggering of inspiratory onset by a cardiovascular afferent(s) associated with a preceding heart beat.[10 11] During a coupled or cardiac-initiated breath, inspiratory onset will occur a fixed interval (the coupling interval, typically 0.5 s) after an ECG R wave. However, the exact relationship between the timing of the ECG R wave and inspiratory onset is complex and will vary according to whether the breath has been initiated by the intrinsic inspiratory pacemaker or by the cardiac trigger. This variation leads to multiple patterns of coupling, which can be described in terms of variation in coupling interval and entrainment ratio (number of heart beats within each breath).[9–11] These patterns have been classified as I, II, III, IV and uncoupled, although other patterns have been suggested both from clinical observation and from computer modelling.[11]

The temporal coherence of heart beats and inspiration is a major determinant of breath-to-breath fluctuations in breathing frequency during anaesthesia.[10] As breathing influences HRV through respiratory sinus arrhythmia, it is to be expected that cardioventilatory coupling will contribute significantly to the pattern of HRV.[9 12 13] By temporally aligning heart beats to the breathing cycle, and given a constant breathing period, heart beats will occur at constant positions within the breathing cycle from breath to breath. Heart beats are therefore subject to repeating patterns of respiratory mediated fluctuations in vagal tone (RSA), giving rise to repeating patterns of HRV. In a previous paper we have demonstrated that, during one particular pattern of coupling (pattern I), the precise positioning of heart beats within each breath results in maximal fluctuations in heart rate due to RSA.[13] We have suggested that, on the basis of these repeating patterns of HRV, it may be possible to detect cardioventilatory coupling from heart rate time series. In a preliminary description we have shown that several geometrical features of heart rate time series may occur in association with cardioventilatory coupling[12], and in the present work we have examined the relationship between three standard measures of HRV and coupling.

Methods

Ethical approval was obtained for all data collection. The 98 subjects, the technique of anaesthesia and the data recording methods have been described in detail in a previous paper on the effect of coupling on ventilatory variability.[10] All subjects were breathing spontaneously during general anaesthesia for elective surgical procedures, had no evidence of cardiorespiratory disease and were taking no medication which was likely to influence autonomic function.

Anaesthesia was induced in all subjects with propofol and maintained with isoflurane, nitrous oxide and oxygen. Opioids were given according to surgical indications. Subjects breathed through a laryngeal mask airway, with F_{IO_2} adjusted to maintain arterial oxygen saturation (Sp_{O_2}) at or above 96% at all times.

We monitored Sp_{O_2}, end-tidal carbon dioxide (Datex Oscar, Datex-Ohmeda, Helsinki, Finland), non-invasive blood pressure (Dinamap) and ECG (lead CM5; Neo-trak 502; Corometrics, Connecticut, USA). Ventilatory timing was measured by an electronically triggered non-return valve within the breathing system. Continuous recordings of ECG and ventilatory timing were made using a Macintosh IIcx computer with a 16-bit ADC board (MIO-16; National Instruments, Austin, TX, USA) and a sampling rate of 500 Hz.

Data analysis

Quantitative and qualitative measures of cardioventilatory coupling

From the ECG and ventilatory timing signals, we determined the time from each R wave to the onset of the following inspiration (RI interval) and plotted successive RI intervals as a time series. Horizontal banding within these RI plots indicates a constant temporal alignment between heart beats and inspiration (i.e. cardioventilatory coupling). The heart beat which immediately precedes inspiratory onset is given a negative subscript (R_{-1}) and the interval between that heart beat and the inspiration is designated the RI_{-1} interval. During coupling, RI_{-1} is generally the most constant RI interval.

Patterns of coupling were defined as follows:

Pattern I: constant RI_{-1} alignment and a constant number of heart beats in each ventilatory period (i.e. constant entrainment ratio);

Pattern II: constant RI_{-1} alignment but with a varying entrainment ratio;

Pattern III: RI_{-1} intervals alternate between two values from breath to breath;

Pattern IV: RI_{-1} interval alignment slowly changes (increases or decreases) from breath to breath, but holds transiently at the RI alignment associated with coupling;

Uncoupled: No consistent RI_{-1} interval alignment observed.

The dispersion of RI_{-1} interval values correlates inversely with coupling. During coupling patterns I and II the RI_{-1} interval will be virtually identical from breath to breath, whereas the RI_{-1} interval varies to a greater degree during coupling patterns III and IV, and in uncoupled time series will give the appearance of randomness. Statistical measures of RI_{-1} dispersion therefore correlate with the degree of heart beat to inspiratory alignment. On the basis of computer modelling of the coupling process, the RI_{-1} dispersion is a measure of the proportion of the breaths which have been triggered by a cardiac signal.[11] In the present study the RI_{-1} interval dispersion was measured using proportional Shannon entropy of the RI_{-1} interval (H_{RI-1}), the details of which have been published previously[14] and are given in the Appendix. Values of H_{RI-1} below 0.7 are typically associated with the appearance of cardioventilatory coupling in RI_{-1} time series plots.

Spectral analysis

To determine the effect of cardioventilatory coupling on spectral measures of HRV, we extracted epochs of data, 256 s in length, displaying as near as possible a constant single pattern of coupling throughout.

Spectral analysis was performed using a method based on that of Akselrod and colleagues,[1 15] which is given in the Appendix. The spectral power (integrated area under the power spectrum curve) was calculated in each subject for total power and in three frequency bands: high (0.15–0.45 Hz), low (0.08–0.15 Hz) and very low (0.02–0.08 Hz). The proportion of the total power in each frequency band was also calculated.

Data epochs for ApEn and D_F

The ApEn and D_F of RR interval time series are generally computed from data series of at least 500–1000 heart beats.[6 8 16] In this study, data epochs of 500 heart beats were used. However, because the pattern and degree of coupling changes over time it was not possible to obtain a sufficient number of 500-heart beat epochs demonstrating a single pattern of coupling throughout for statistical analysis. We therefore extracted a single 500-beat epoch of heart rate time series from as many subjects as possible, without reference to the RI plot. A maximum of one epoch was extracted from each subject and, where possible, the heart rate time series was free of non-stationary trends.

For each epoch of heart rate data, we determined ApEn and D_F and calculated H_{RI-1} from the associated RI interval plot. ApEn was calculated using the algorithm of Pincus[5] and D_F was calculated using the method of Katz;[3] both of these methods are given in the Appendix.

Analysis

Data were acquired and variables were calculated using custom-written software in LabVIEW 5 (National Instruments, Austin, TX, USA). Statistical analysis was performed using Statview 5.

We used the Kruskal–Wallis test to examine the relationship between the total spectral power and the proportions of power in the high-, low- and very low-frequency bands, and the different patterns of coupling.

We examined the relationship between H_{RI-1} and total spectral power, proportional band power, D_F and each of the ApEn scores (for m=2 as well as m=3, at r^{En}=0.025, 0.05, 0.075, 0.1, 0.15, 0.2, 0.3, 0.4, 0.5 and 0.6; m is the number of heart periods in a sequence and r^{En} is the tolerance range within which sequences of m RR intervals are considered to be similar) using the Spearman rank correlation.

Results

Cardioventilatory coupling was observed in all subjects, although, as we have described previously,[10] the duration and degree of coupling varied considerably over time and between individuals. We extracted 70 epochs of 256 s for spectral analysis where a single coupling pattern dominated throughout the epoch. Where other patterns were interspersed briefly within these epochs, we ensured that these periods occurred towards the beginning or end of the selected epoch in order to minimize the effect on the Fourier analysis. These spectral epochs comprised 12 pattern I, 21 pattern II, 6 pattern III, 9 pattern IV and 23 uncoupled. For ApEn and D_F analysis, we obtained 52 epochs of 500 heart beats meeting the criteria for ectopy and stationarity.

Spectral analysis

No significant difference in total spectral power was observed between the different patterns of coupling. However, there was a significant difference in the distribution of power, with a significantly greater proportion of power in the low-frequency band and a corresponding decrease in the proportion of high-frequency power observed in pattern II coupling epochs. This observation was related to the expected[10] low breathing frequency in epochs with pattern II coupling (Table 1). As the breathing frequency decreased, movement of the high-frequency respiratory-related spectral peak into the range of the low-frequency band (defined as 0.08–0.15 Hz) occurred, resulting in an apparent increase in low-frequency power in this group. If we exclude pattern II epochs, there were no significant differences in distribution of power between epochs of different coupling patterns.

Figure 1 shows an example of heart rate, respiratory frequency and RI interval time series, as well as power spectra of HRV for an epoch of pattern I coupling and an uncoupled epoch. Pattern I coupling is seen in the RI interval plot in (Fig. 1A), where a constant temporal relationship between heart beats and inspiration (occurring at time=0) was observed, with a constant three heart beats per breath. In contrast, there is no apparent structure in the RI interval plot in (B). The two power spectra demonstrate that, for both of these epochs, the vast majority of power was in the high-frequency band (at the respiratory frequency).

No significant correlation was observed between H_{RI-1} and the total HRV power, or proportion of power in the high-, low- and very low-frequency ranges in the group of epochs comprising patterns I, III, IV and uncoupled.

Table 1 Comparison of mean RR interval (mean RR), mean consecutive difference RR interval (mean CD RR), mean respiratory frequency (mean *f*), total spectral power 0.02–0.45 Hz (total power) the percentage power in the high, low and very low frequency bands (% high, % low, % very low) according to coupling pattern. Values given are mean (SD) Groups were compared with ANOVA (mean RR, mean CD RR, *f*, % power) or the Kruskil–Wallis test (total power) Where differences were identified, the unpaired *t*-test was used to compare differences between groups. * denotes significantly different compared to pattern I, † denotes significantly different compared to pattern II, ‡ denotes significantly different compared to pattern IV

	Pattern I	**Pattern II**	**Pattern III**	**Pattern IV**	**Uncoupled**	***P***
n	12	21	6	9	23	
Mean RR	0.94 (0.10)	0.98 (0.15)	0.87 (0.04)	0.81 (0.13)*†	0.94 (0.16)‡	0.03
Mean CD RR	0.035 (0.020)	0.024 (0.012)	0.033 (0.020)	0.022 (0.017)	0.030 (0.017)	n.s.
Mean *f*	18.3 (4.0)	12.0 (3.1)*	20.4 (0.4)†	20.2 (2.0)†	19.9 (5.4)†	0.0001
Total power	0.025 (0.023)	0.012 (0.009)	0.026 (0.026)	0.013 (0.017)	0.019 (0.020)	n.s
% High	96.1 (4.0)	88.7 (10.4)*	95.1 (7.1)	97.3 (3.4)†	96.6 (2.5)†	0.0006
% Mid	2.1 (1.9)	9.3 (10.4)*	2.1 (2.0)	1.2 (1.6)†	2.0 (1.6)†	0.0003
% Low	1.6 (2.1)	1.9 (1.3)	2.5 (1.3)	1.2 (1.4)	1.2 (1.0)	n.s.

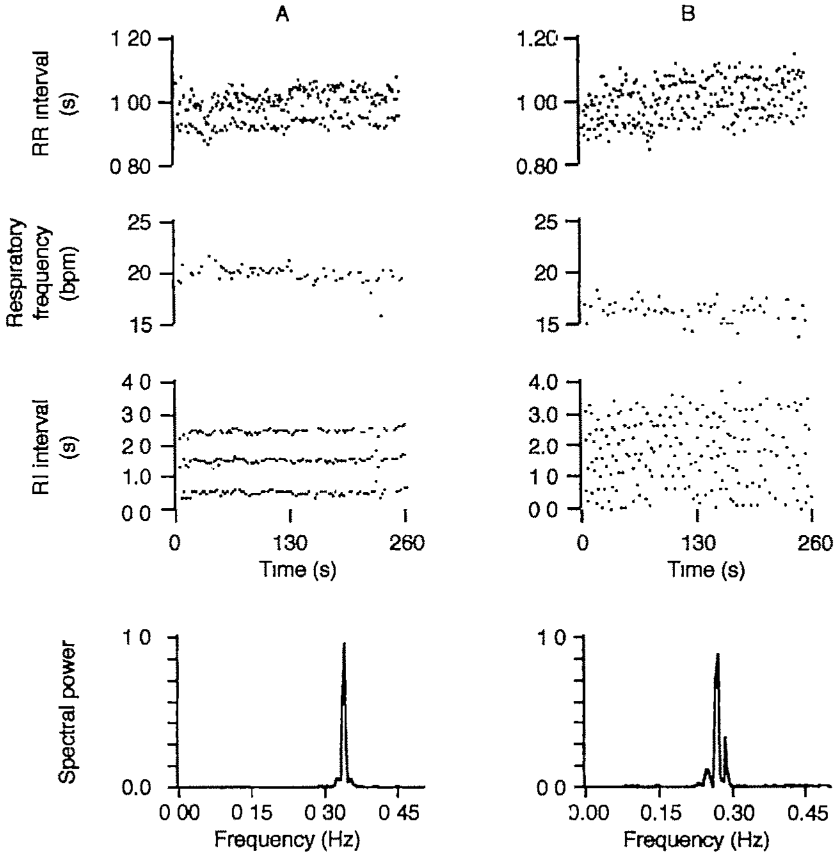

Fig 1 Representative plots of RR interval, respiratory frequency, RI interval and power spectra for (A) a pattern I coupling epoch and (B) an uncoupled epoch

Approximate entropy

We observed no correlation between $H_{\mathrm{RI-I}}$ and ApEn for any combination of *m* or *r* values selected in this study (Table 2). ApEn correlated negatively with RR interval at r=0.025 for both m=2 and m=3 and positively with RR interval at 0.075, 0.1, 0.15 and 0.2 for both m=2 and m=3. We also observed a negative correlation between respiratory frequency and ApEn at all values of *m* and r^{En} with the exception of r= 0.025 for both m=2 and m=3, where no significant relationship was observed. The high-frequency spectral power correlated with all ApEn values except for that at r^{En}=0.05 with m=2 or 3; for low r^{En} values the correlation was negative and for values above 0.05 it was positive.

Fractal dimension

We observed no correlation between D_F and $H_{\mathrm{RI-I}}$. D_F correlated (1) positively with mean RR interval (P<0.05); (2) with all ApEn values except for that at r= 0.075 with m=2 or r=0.05 and 0.075 for m=3; this correlation was

Table 2 Correlation between ApEn and RR interval, respiratory frequency, H_{RL-1}, high-frequency (HF) power and D_F from the 500 heart beat epochs. Spearman rank correlation coefficient (ρ) is given for ApEn *vs* mean RR interval, mean respiratory frequency, proportional Shannon entropy of the RL_{-1} interval (H_{RL-1}), high-frequency power and D_F *P=0.05, **P=0.01; ***P=0.005; ****P<0.001; n.s. = not significant

m	r^{En}	Mean RR	Mean f	H_{RL-1}	HF power	D_F
2	0.025	−0.323*	n.s.	n.s.	−0.64****	−0.560****
2	0.05	n.s.	n.s.	n.s.	n.s.	0.287*
2	0.075	0.302*	−0.313*	n.s.	0.37*	n.s.
2	0.1	0.297*	−0.315*	n.s.	0.46***	0.334*
2	0.15	0.270*	−0.297*	n.s.	0.49****	0.394*
2	0.2	0.304*	−0.300*	n.s.	0.53****	0.384**
2	0.3	n.s.	−0.274*	n.s.	0.48***	0.361*
2	0.4	n.s.	−0.263*	n.s.	0.51****	0.395**
2	0.5	n.s.	n.s	n.s.	0.49****	0.382**
2	0.6	n.s.	−0.284*	n.s.	0.47***	0.395**
3	0.025	−0.339*	n.s.	n.s.	−0.68****	−0.607****
3	0.05	n.s.	n.s.	n.s.	n.s	n.s
3	0.075	0.307*	−0.304*	n.s.	0.36*	n.s.
3	0.1	0.287*	−0.298*	n.s	0.44***	0.321**
3	0.15	0.262*	−0.295*	n.s.	0.49****	0.366**
3	0.2	0.297*	−0.309*	n.s	0.52****	0.375**
3	0.3	n.s.	−0.271*	n.s.	0.47***	0.361*
3	0.4	n.s.	n.s.	n.s	0.51****	0.398***
3	0.5	n.s	n.s.	n.s	0.49****	0.382**
3	0.6	n.s.	−0.285*	n.s.	0.46***	0.384**

negative for r=0.025 and positive for the higher values; (3) positively with high-frequency spectral power (ρ=0.93, P<0.0001) and the proportion of power in the high-frequency band (ρ=0.57, P<0.0001); and (4) inversely with age (ρ=−0.36, P=0.02). D_F did not correlate with respiratory frequency.

Discussion

In this study we explored the relationship between cardioventilatory coupling and standard spectral and non-linear measures of HRV. We examined heart rate time series from clinical subjects, identified the specific coupling pattern and measured coupling using entropy of the RL_{-1} interval. We observed no correlation between cardioventilatory coupling and any of the frequency and non-linear domain measures of HRV used.

RSA is determined by ventilatory phase-related vagal modulation. The degree of modulation is influenced by a variety of factors, including age, position, underlying vagal tone and respiratory frequency.[17] Vagal tone is reduced soon after inspiratory onset, causing a brief acceleration in heart rate. Vagal tone then returns and heart rate decreases before the onset of the next inspiration. The vagal modulation, and hence heart rate variation, is therefore cyclic, with a maximum and minimum heart rate at specific phases of the breathing cycle. This cyclic RSA response can be demonstrated in the form of an RSA curve, where the duration of the RR interval between two consecutive R waves (R_n and R_{n+1}) is plotted against the time that R_{n+1} occurs after inspiratory onset (or against the phase of the ventilatory cycle). Coupling relates to this curve in at least two ways.

First, in the majority of individuals with pattern I coupling, the two consecutive R waves which immediately follow inspiratory onset (R_{+1} and R_{+2}) tend to fall at the extremes of the RSA curve.[13] R_{+1} is therefore preceded by the longest RR interval and R_{+2} is preceded by the shortest RR interval that can occur for the particular RSA curve. This leads to an apparent maximization of RSA; that is, for most breaths the difference between the maximum and minimum RR intervals within the breath is as great as is possible for the given RSA curve. It would be expected that this would lead to an increase in power in the high (respiratory) frequency band. That we did not observe this in our pattern I data epochs may relate to at least two factors: (1) we know that the effect does not occur in all subjects;[13] and (2) high-frequency power is already high and there is a wide inter-individual difference in spectral power; because the numbers of epochs with pattern I of sufficient length were small, it is therefore difficult statistically to detect significant variation in high-frequency power.

The absence of a relationship between coupling and distribution of spectral power suggests that the coupling pattern is independent of cardiac autonomic tone. This observation is consistent with our demonstration that the coupling pattern is determined by the ratio of heart rate to intrinsic breathing frequency as well as the magnitude of the cardiac-related afferent trigger.[11]

The HRV power spectrum will be influenced by factors other than autonomic tone. For example, the position and character of the high-frequency peak will be influenced by ventilatory frequency fluctuations. As coupling, specifically the coupling pattern, determines much of the ventilatory variability of spontaneously breathing anaesthetized subjects, the coupling pattern should affect the characteristics of the respiratory spectral peak. These minor effects are, however, beyond the scope of this paper.

The second relationship between the RSA curve and coupling arises because coupling is a triggering of inspiratory onset by cardiac activity and therefore inspiration is temporally aligned to the preceding, triggering heart beat (usually RL_1). It follows that each of the subsequent heart beats (R_{+1}, R_{+2}, etc.) will also align themselves to the preceding inspiratory onset. Thus each heart beat will become aligned to constant phases of the ventilatory cycle. Each heart beat within a ventilatory cycle will therefore be modulated differently according to its position on the RSA curve. In pattern I coupling, where the entrainment ratio remains constant (i.e. there is a constant number of heart beats within each ventilatory period), identically repeating sequences of HRV will occur with each breath. One observes this repetition as discrete banding of the RR interval time series.[12] Coupling should therefore be associated with regularity of the heart rate time series. To a degree, this regularity may be disrupted if the entrainment ratio is varying from breath to breath, as it does in coupling patterns II, III and IV. Thus, although regularity should be a feature of HRV during pattern I coupling, this may be less likely for patterns II, III and IV and uncoupled epochs.

It has been suggested that ApEn has value in distinguishing between 'regularity' in HRV under pathophysiological conditions and greater 'irregularity' in HRV in 'normal' individuals.[18 19] ApEn is, however, a family of statistics, and its correlation to any physiological process will depend upon the selection of values for N (number of RR intervals), m and r.[6] In the present study the correlation between ApEn and D_F or high-frequency spectral power (i.e. RSA) was critically dependent upon the selection of r^{En} in the range 0.025–0.075. It is possible that this dependence on the control variables may lead to entirely different conclusions. Thus, Palazzolo and colleagues[16] observed a good correlation between ApEn (N=2048, m=2, r=0.07) and the high-frequency spectral component of HRV in resting dogs and found that sympathetic blockade did not alter ApEn, whereas parasympathetic blockade produced significant decreases in ApEn. It was therefore concluded that ApEn was positively related to RSA. In contrast, Mansier and colleagues[4] computed ApEn (N=1000, m=2, r=0.05) in the mouse and found that the administration of atropine was associated with a significant increase in ApEn. The authors noted that there was a decrease in the total variability associated with atropine treatment, as measured by spectral analysis, but that the 'complexity' of the series increased according to ApEn and other non-linear measures. These authors therefore concluded that ApEn was inversely related to RSA. It seems probable that the divergent opinions of Mansier and Palazzolo can be explained by their choice of control variables.

ApEn did not correlate with the dispersion of the RL_1 interval (i.e. cardioventilatory coupling) at either m=2 or m=3 for any of the r^{En} values used in the present study. As coupling is associated with repeating geometrical patterns of HRV[12] and ApEn is said to be a measure of regularity, this observation was surprising. Several explanations will now be considered.

(1) Coupling during anaesthesia is characterized by rapid transitions between coupling patterns, which are in turn determined by the heart rate/breathing frequency ratio.[10 11] Each coupling pattern is associated with a different entrainment ratio variation from breath to breath. As the entrainment ratio variation will alter the position of heart beats on the RSA curve, transitions in coupling pattern will therefore disrupt the regularity of HRV and could thereby alter ApEn.

(2) In clinical time series, non-stationarity (an overall trend) in the heart rate time series is difficult to avoid. Thus, although repetitive patterns may occur throughout the time series, in the presence of trend they will fall outside the tolerance r^{En}. In order to reduce this effect, we also examined the correlation between ApEn and H_{RI-1} where ApEn was measured (for all 20 combinations of m and r^{En}) from the RR interval consecutive time series [i.e. (rr_2–rr_1), (rr_3–rr_2), (rr_4–rr_3)... (rr_n–rr_{n-1})]. As with the ApEn derived from the raw RR time series, however, no significant correlation was found.

(3) In some subjects the magnitude of RSA is small and, as in paragraph (2) above, any small variation in HRV due to noise will mask the pattern repetition and cause repeating patterns to fall outside the tolerance r^{En}.

(4) It is possible that dispersion of the RL_1 interval, as measured by its Shannon entropy, is itself limited as a measure of coupling. In a previous paper we have demonstrated that H_{RI-1} correlates well with the appearance of coupling in the RI interval plot, in particular during patterns I and II. During coupling patterns III and IV, however, where RL_1 dispersion is greater, the difference in H_{RI-1} with uncoupled epochs is measurable but small. However, it should noted that ApEn and D_F did not differ between pattern I and uncoupled epochs. In addition, having observed the lack of correlation between ApEn and H_{RI-1}, we also examined the correlation between the set of 20 ApEn values and other measures of RL_1 dispersion, although none correlated significantly with any value from the ApEn set (these measures included the proportional Shannon entropy derived from all RL_1 intervals in each epoch rather than the median of the 10-breath moving window; RL_1 standard deviation; mean RL_1 consecutive difference; and standard deviation RL_1 consecutive difference).

(5) ApEn measures the log likelihood that short epochs of data with a similar pattern will *remain* similar as the epoch length is increased. As coupling is associated with repetition of a specific pattern, a statistic which examines the likelihood that a pattern *is* similar might be a better correlate with coupling. ApEn may therefore be measuring a quality of RR variability different from that resulting from coupling.

In conscious subjects, Yeragani and colleagues[20] observed that D_F was positively correlated to both ApEn and high-frequency spectral power, suggesting that both measures reflected parasympathetic modulation of heart rate, and on this basis it was suggested that the two measures (ApEn and D_F) could be used interchangeably. Similar results were reported by Jartti and colleagues.[8] In the present study we found high correlations between D_F and ApEn, as suggested by Yeragani and colleagues, at values of $r^{En} \geqslant 0.05$, although, as noted above, at lower values of r an inverse relationship is seen. Both D_F and ApEn strongly correlated with high-frequency power and therefore it is probable that the dominant influence on each of these measures is RSA. As with ApEn, we observed no relationship between D_F and cardioventilatory coupling.

In conclusion, using standard spectral and non-linear measures of HRV we were unable to demonstrate an effect of cardioventilatory coupling on heart rate time series. However, graphical displays of clinical time series plainly show that, during periods of coupling, the heart rate time series may take on a qualitative appearance which is different from that observed in uncoupled time series. Alternative analytical techniques are therefore desirable for the detection of coupling in heart rate time series, and these are explored in the accompanying paper.[21]

Appendix

Measures of cardioventilatory coupling and HRV

Proportional RL_1 Shannon entropy (H_{RI-1})

The RL_1 interval dispersion was measured using proportional Shannon entropy of the RL_1 interval (H_{RI-1}). Starting from the beginning of each RL_1 interval time series, we used a 10-breath moving window and placed the corresponding RL_1 intervals within each window into a 10-bin histogram with outer limits set at 0 and the mean of the RR intervals which had been encompassed by the 10 inspiratory onsets. From the bin occupancy of this histogram, we calculated H_{RI-1} as follows:

$$\text{Shannon entropy} = H = -\sum_{b=1}^{N} Pb * \log(Pb)$$

$$\text{Maximum Shannon entropy} = H_{\max} = -\log(1/N)$$

$$H_{RI-1} = H/H_{\max}$$

where P is the actual histogram bin probability, b is the bin number and N is the number of histogram bins.

The median value from successive moving windows over the entire RL_1 time series was used as a measure of RL_1 dispersion. Values below 0.7 are typically associated with the appearance of cardioventilatory coupling in RL_1 time series plots.[14]

Spectral analysis

To determine the effect of cardioventilatory coupling on spectral measures of HRV, we extracted epochs of data, 256 s in length, displaying as nearly as possible a constant single pattern of coupling throughout.

Spectral analysis was performed using a method based on that of Akselrod and colleagues.[1 15] The 256-s RR interval time series, free of ectopy, was sampled at the rate of 4 Hz to produce a series of 1024 discrete RR interval values. This series was then high-pass filtered to remove fluctuations less than 0.015 Hz and low-pass filtered at 2 Hz to remove components at greater than Nyquist frequency. A fast Fourier analysis was performed using a Hanning window. The spectral power (integrated area under the power spectrum curve) was calculated in each subject for total power and in three frequency bands: high (0.15–0.45 Hz), low (0.08–0.15 Hz) and very low (0.02–0.08 Hz). The proportion of the total power in each frequency band was also calculated.

Approximate entropy (ApEn)

ApEn was calculated using the algorithm of Pincus.[5] Starting from the first RR interval, a segment or window of m heart periods is taken, these forming a short sequence of RR interval variation. The entire RR time series is then examined for sequences with similar values (within a tolerance of r^{En}) and the number of similar sequences is counted. The window is then moved to the next consecutive RR interval and the number of similar sequences to this is then computed. This procedure is repeated as the window moves across the time series. The resulting count is then compared with a similar count for the sequence value (m+1). In this manner, ApEn measures the log likelihood that runs of data with a particular pattern will retain the same pattern for the next incremental observation. To compute ApEn, three input values must be decided according to the variables: (1) the number of data points (N) to be analysed, in this study N=500 heart beats, as discussed above; (2) the 'embedding dimension' (sequence length m) for comparison (for heart rate time series, m=2 and m=3 are the most commonly used embedding dimensions)[6 7 16] and in the present study ApEn values were computed for both m=2 and m=3; (3) the tolerance range (r^{En}) within which sequences of m RR intervals are considered to be similar. Values of r^{En} are typically expressed as a fraction of the standard deviation of the RR interval time series and values in the range 0.05–0.25 are generally used.[5–7 16] However, to prevent missing a correlation with coupling resulting from selecting inappropriate r^{En} values, we chose to use a range of r values wider than is normally used, selecting r^{En}=0.025, 0.05, 0.075, 0.1, 0.15, 0.2, 0.3, 0.4, 0.5 and 0.6 of the standard deviation of the RR interval time series. Thus, for our 500-beat time series, ApEn was calculated for 20 combinations of m and r^{En}.

Fractal dimension (D_F)

D_F was calculated using the method of Katz:[3]

$$D_F = \log(n)/[\log(n) + \log(d/L)]$$

where n is the number of data points, d is the planar extent of the curve (the 'distance' in time from the starting point to the *n*th point) and L is the total length of the curve. This algorithm generates a value for D_F between 1 (representing a signal with low space-filling capacity) and 2 (representing a signal with high space-filling capacity).

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Cardioventilatory coupling in heart rate variability: methods for qualitative and quantitative determination

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In this study we sought to develop quantitative methods for determining the presence of cardioventilatory coupling in raw heart rate time series. The beat-to-beat RR interval time series of 98 anaesthetized, spontaneously breathing subjects were represented graphically as (1) raw RR interval time series, (2) RR consecutive difference time series and (3) a phase portrait of the RR consecutive difference time series. We then examined the relationships between the presence of cardioventilatory coupling in these epochs and the plot appearance and entropy measures derived from these plots. We observed that coupling was significantly associated with the presence of banding in the raw heart rate and RR consecutive difference time series, and with discrete clustering within the RR consecutive difference phase portrait. A significant correlation was found between coupling and the entropy of the RR consecutive difference time series and its phase portrait. We conclude that, with some provisos, these simple graphical and derived quantitative measures provide a basis for the determination of cardioventilatory coupling from heart rate time series.

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Cardioventilatory coupling is a mechanism whereby heart beats entrain the respiratory rhythm, triggering inspiratory onset by an as yet unknown cardiovascular afferent pathway or pathways.[1–4] This form of pacing by the heart is a major determinant of inspiratory timing and breathing rate variability during spontaneous-breathing general anaesthesia.[5] From an analysis of the complex relationship between heart beat and inspiratory timing and by applying modelling techniques to the interaction, we have concluded that inspiratory triggering by heart beats is not invariable during cardioventilatory coupling.[4 5] Under some circumstances consecutive breaths are initiated by the cardiac activity, but at other times the cardiac-triggered breaths may be mixed with breaths that have been initiated spontaneously by the intrinsic respiratory pacemaker. The numerical sequence pattern of cardiac and intrinsically generated breaths is seen as a coupling pattern, this pattern defining the relationship between heart beat and inspiratory timing. Although we have classified the most common patterns numerically (patterns I, II, III and IV and uncoupled),[1] it is probable that these make up part of a much larger family of possible triggering sequences.[4] During general anaesthesia, coupling patterns may change from moment to moment or may remain stable for an hour or more.[1 5] Although coupling patterns appear to vary in a random manner, we have shown that the specific coupling pattern is determined by the fractional component of the ratio of heart rate to the rate of the intrinsic respiratory oscillator (e.g. with a ratio of 3.85 the coupling pattern is determined by the 0.85).[1 4 5]

In addition to cardioventilatory coupling, the timing interaction between breathing and the heart beat is also governed by respiratory sinus arrhythmia (RSA).[6 7] The mutually interactive combination of cardioventilatory coupling and RSA forms a complex feedback system; the heart beat affects breathing and breathing affects the heart beat. It is important to appreciate, however, that these processes are distinct; one is not simply the converse of the other. In cardioventilatory coupling, a heart beat *triggers* inspiratory onset[1–4] and in RSA the breathing cycle *modulates* the heart rate.[6 7]

Although coupling primarily influences inspiratory timing, coupling should also influence the pattern of heart rate variability (HRV). This follows because coupling determines the timing of inspiratory onset, which in turn determines the onset of vagal modulation by RSA. Consistent with this, we have identified geometrical features of the heart rate time series that are clearly associated with coupling.[8] In contrast, we have been unable to demonstrate

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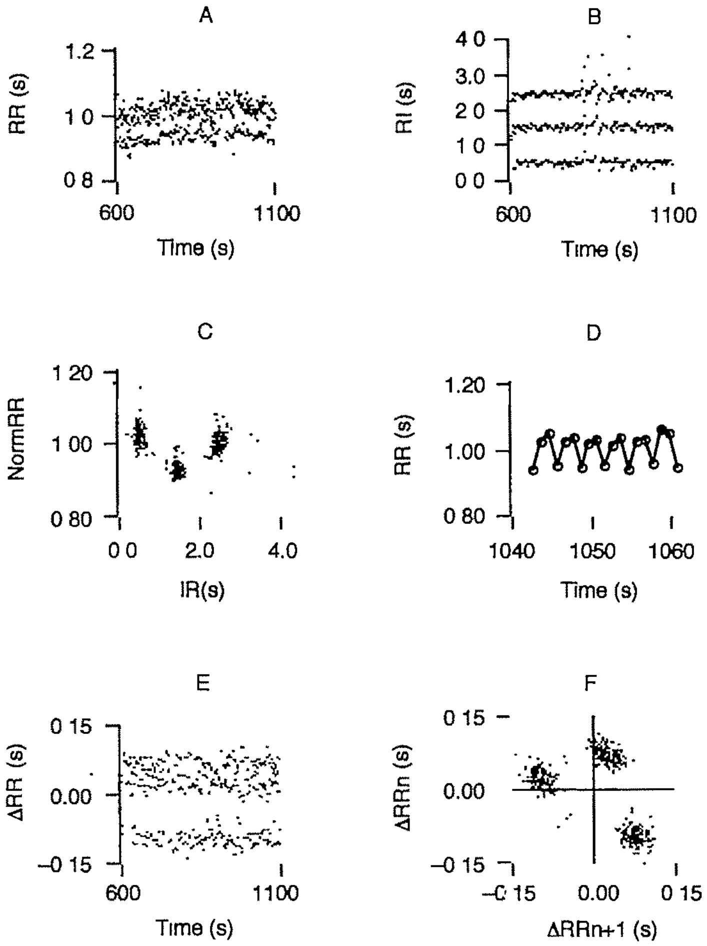

Fig 1 A 500-s epoch from a subject exhibiting 3:1 cardioventilatory coupling. (A) RR interval time series showing two distinct bands. (B) RI interval plot showing pattern I cardioventilatory coupling. (C) Normalized preceding RR interval plotted against the time an R wave occurs after inspiratory onset (IR interval) Note the clustering of heart beats in constant relationship with inspiratory onset (at t=0). (D) Representative detail of the variation in RR interval (E) Consecutive difference time series (ΔRR_n, ΔRR_{n+1}, . .) Two distinct bands are visible. (F) Consecutive difference phase portrait plot (ΔRR_n vs ΔRR_{n+1}). Three distinct clusters are seen, each corresponding to the variation between three consecutive RR intervals.

any statistical correlation between coupling and standard measures of HRV, such as the distribution of spectral power, approximate entropy or the fractal dimension.[9] In the present paper we elaborate on the observation of geometrical patterning in heart rate time series during coupling and we attempt to derive simple quantitative measures of HRV that could be used to suggest the presence of coupling from the heart rate time series.

Methods

Data were taken from the intraoperative records of 98 adult subjects undergoing minor surgical procedures under spontaneous-ventilation general anaesthesia. The anaesthetic technique, inclusion criteria and methods of monitoring and data-gathering are described in the companion paper.[9] We recorded digitally at 500 Hz to a Macintosh IIcx computer an ECG R wave and inspiratory onset time series during spontaneous-ventilation general anaesthesia.

Cardioventilatory coupling

To demonstrate cardioventilatory coupling, we determined the time of each R wave peak from the ECG and the start of each inspiration. We then calculated the time interval between each R wave and the following inspiratory onset (RI interval). The RI intervals were then plotted against time of R wave occurrence (RI plot). A fixed relationship between heart beats and inspiration (cardioventilatory coupling) is seen in an RI plot as horizontal banding in which the R wave, in particular that which immediately precedes inspiration, falls in constant temporal relationship with inspiratory onset (Fig. 1).

Extraction of data epochs

We extracted two epoch types from the recorded data.

Coupling pattern epochs

In order to examine the correlation between a particular coupling pattern and the geometry of the heart rate time series, we selected periods from the RI time series, without any visual reference to the HR time series, in which the pattern of coupling was stable. Epoch patterns were classified, as previously described, as uncoupled or patterns I–IV.[1 4 5] The minimum coupling pattern epoch length was 50 s and between one and three epochs were extracted from each subject. No two identical patterns were selected from any one subject. These epochs differed from the 256-s coupling pattern epochs used to examine the relationship between spectral measures of HRV and cardioventilatory coupling in the companion paper[9] as we were no longer constrained by the requirements of the Fourier transform to use a 2^n data set. The use of shorter coupling pattern epochs ensured that these were uncontaminated by other coupling patterns, and a greater number could be obtained from the available data sets.

500-beat RR interval epochs

In any extended HR time series, the pattern of coupling may vary from moment to moment according to a mathematical relationship between the HR and intrinsic breathing frequency.[4 5] In order to examine a randomly sampled HR time series for the presence of coupling, we therefore extracted from each subject a single HR epoch, without reference to the RI plot. These epochs were all 500 heart periods in length and were free of rhythm abnormalities, and up to one epoch was extracted from subjects who provided data of suitable length. Where possible, the heart rate time series was chosen to minimize non-stationarity. The relationship between standard non-linear methods of HRV analysis and cardioventilatory coupling in these same epochs is examined in the companion paper [9].

RSA curves

For all epochs, we plotted, for each R wave, the immediately preceding RR interval against the time that the R wave occurred after the preceding inspiratory onset (Figs 1 and 2). These 'RSA curves' reveal the effect of vagal modulation on RR interval and the positioning of R waves relative to inspiratory onset.

Entropy of the RI_{-1} time series

As a quantitative measure of coupling, we determined for each epoch the dispersion of the RI_{-1} interval (the interval between inspiratory onset and the immediately preceding the R wave). These RI_{-1} intervals were then placed in a 10-bin histogram between limits 0 and mean $RR_{-1/+1}$ s, where $RR_{-1/+1}$ is the duration of the RR interval that spans inspiratory onset. The resulting histogram was examined using a measure of entropy (Shannon entropy). In a manner not dissimilar to that of the χ^2 statistic, Shannon entropy compares the actual bin occupancy against the expected bin occupancy for a series of RI_{-1} intervals that are evenly distributed between histogram bins. Shannon entropy of the RI_{-1} distribution equals 0 if all RI_{-1} intervals fall into a single bin (perfect coupling, in which every breath is cardiac-triggered) and a maximum finite value if they are equally distributed between bins.[2 9] Proportional Shannon entropy of the RI_{-1} distribution (H_{RI-1}) is the calculated Shannon entropy divided by the maximum value, and it ranges between 0 (perfectly coupled) and 1 (uncoupled). For each data epoch, we passed a 10-point moving window through the RI_{-1} time series, calculating H_{RI-1} for the distribution of RI_{-1} intervals within each window. The median of the H_{RI-1} from these windows was taken as a quantitative measure of coupling for that epoch.

Graphical RR interval plots

From the RR interval time series for each coupling pattern epoch and for each 500-beat epoch we calculated and plotted the following variables: (1) raw RR interval (rr_1, rr_2,.... rr_x) against time; (2) RR interval consecutive differences [(rr_2–rr_1), (rr_3–rr_2),... (rr_x–rr_{x-1})] against time (Δrr_n); and (3) RR consecutive difference phase portrait, i.e. RR consecutive difference plotted against the following consecutive difference (rr_n–rr_{n-1}) plotted against (rr_{n+1}–rr_n), i.e. (Δrr_n *vs* Δrr_{n+1}).

Qualitative description of structure within the RR interval coupling pattern epochs

Two independent observers examined the three graphical plots derived from the coupling pattern epochs without reference to any other information. For raw RR and consecutive difference RR time series, the observers noted the presence of banding, and in the RR consecutive difference phase portrait they noted the presence of discrete clusters. Banding or clustering was considered present only when the two observers were in agreement.

Quantitative measures derived from the RR interval plots

In a manner similar to that described for calculating the H_{RI-1} for the RI time series (see above), we applied Shannon entropy as a measure of 'structure' to the three forms of RR interval time series plots.

RR interval (rr_1, rr_2,... rr_x) against time

H_{rr} was calculated as the median proportional Shannon entropy for a moving window of 50 RR intervals with histogram limits set at the minimum and maximum values of the RR interval within that window.

RR consecutive differences (Δrr_n) against time

H_{CD} was calculated as the median proportional Shannon entropy for a 50-Δrr moving window, with histogram limits set at the minimum and maximum values of Δrr within that window.

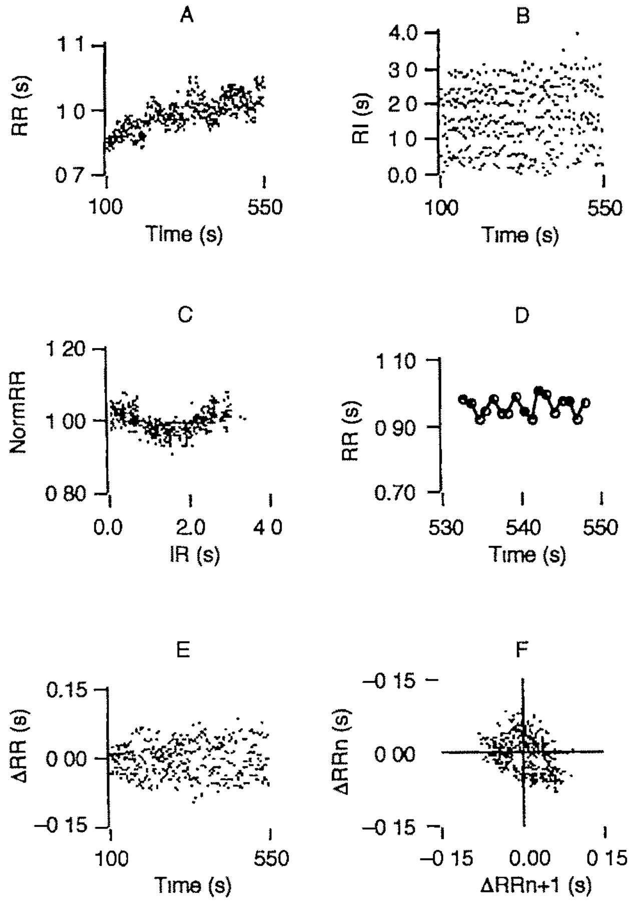

Fig 2 A 450 s epoch from a subject in the absence of cardioventilatory coupling. (A) RR interval time series showing no banding. (B) RI interval plot showing no consistent timing relationship between R waves and inspiration, i.e. an uncoupled time series (C) Normalized preceding RR interval plotted against the time an R wave occurs after inspiratory onset (IR interval). (D) Representative detail of the variation in RR interval. (E) Consecutive difference time series (ΔRR_n, ΔRR_{n+1},) No banding is visible. (F) Consecutive difference phase portrait plot (ΔRR_n *vs* ΔRR_{n+1}) A concentric ring shape is apparent.

Consecutive difference phase portrait (Δrr_n vs Δrr_{n+1})

H_{CDP} was calculated from the distribution of points within a square, the boundaries of which encompassed points ranging between the 2.5 and 97.5% of the Δrr_n range. The square was divided into a 10×10 matrix and the distribution of points within the cells of this matrix was treated as a 100-bin histogram and the H_{CDP} calculated as the proportional Shannon entropy of this distribution.

Statistical analysis

All entropy values were treated as non-parametric variables. Statistical analysis included non-parametric analysis of variance (ANOVA) (Kruskal–Wallis), the Mann–Whitney *U*-test, the χ^2 test and the Spearman correlation, as appropriate. P<0.05 was considered significant.

Table 1 Correlations between coupling (H_{RI-1}) and entropy measures derived from heart rate time series. Values given are P values for correlation (Spearman rank correlation) between H_{RI-1} and entropy measures derived from the heart rate time series

		H_{rr}	H_{CD}	H_{CDP}
Coupling pattern epochs	H_{RI-1}	0.062	0.0001	0.0001
500-heart beat epochs	H_{RI-1}	0.52	0.01	0.03

Raw data were extracted with purpose-written software in LabView 5.1 (National Instruments, Austin, TX, USA) and statistical analysis was performed using Statview 4.0 (SAS Institute, Cary, NC, USA).

Results

From the 98 intraoperative time series, we were able to extract 52 epochs of 500 heart beats and 165 coupling pattern epochs (pattern I, 35; pattern II, 51; pattern III, 16; pattern IV, 26; uncoupled, 37).

Figures 1 and 2 show the RI interval plot, RR interval time series, consecutive difference time series, phase portrait, consecutive difference phase portrait and RSA curves for a representative pattern I and uncoupled epoch respectively.

Table 1 gives the P values for the statistical correlation between the measure of coupling (H_{RI-1}) and entropy measures derived from the graphical plots of HRV. In Table 2, the percentage of coupling pattern epochs displaying qualitative structure is given and the median values for the derived quantitative entropy measures are compared.

Effect of coupling on the RR interval time series plot

RR interval banding was significantly related to the presence of coupling and varied according to the specific coupling pattern. Banding was observed in 37% of pattern I epochs, diminished with other coupling patterns and occurred least (5%) in uncoupled epochs (Table 2). An example of RR time series banding during pattern I coupling is shown clearly in Fig. 1A. This RR interval time series plot shows two distinct bands, a wide band centred a little over 1.0 s and a narrow band beneath the first. In contrast, a representative uncoupled RR interval time series (Fig. 2B) shows a single band within which all RR intervals are distributed. On closer examination of the RR time series, the mechanism of this banding was found to be related to the timing of heart beats relative to the RSA curve. In all subjects studied, the RSA curve showed the expected acceleration in heart rate after the onset of inspiration (Figs 1C and 2C), but the magnitude of this variation differed between subjects according to the degree of RSA present. In the majority of pattern I coupling epochs, the constant alignment of R waves, relative to inspiratory onset, caused R waves to fall at the same positions within the RSA curve

Table 2 Qualitative observations and quantitative measures of structure of heart rate time series according to coupling pattern. Qualitative: for each coupling pattern, numbers represent the percentage of epochs in which banding or clustering was observed. Quantitative measures: H_{rr} is the Shannon entropy derived from the RR interval time series, H_{CD} is the Shannon entropy derived from the consecutive difference RR interval time series, H_{CDP} is the Shannon entropy derived from the consecutive difference phase portrait and H_{RI-1} is the Shannon entropy of the RI_{-1} intervals and is a measure of the strength of cardioventilatory coupling. Values are median (range). Qualitative data were analysed by contingency table analysis, and quantitative data were analysed across the five groups with the Kruskal–Wallis test; where differences were found to be significant we made between-group comparisons using the Mann–Whitney *U*-test. *Significantly different compared with pattern I, †significantly different compared with pattern II, ‡significantly different compared with pattern III; §significantly different compared with pattern IV; n.s. = not significant

	Pattern I (n=35)	Pattern II (n=51)	Pattern III (n=16)	Pattern IV (n=26)	Uncoupled (n=37)	P
Qualitative						
RR interval banding	37	23	31	12*	5*	0.009
RR CD banding	54	41	50	20*†‡	11*†‡	0.0005
ΔRR phase portrait clusters	62	42*	60	32*‡	11*†‡§	0.0001
Quantitative						
H_{rr}	0.93 (0.76–0.98)	0.93 (0.83–0.97)	0.93 (0.89–0.97)	0.93 (0.43–0.98)	0.94 (0.54–0.98)	n.s.
H_{CD}	0.88 (0.58–0.97)	0.88 (0.39–0.96)	0.91 (0.8–0.99)*†	0.93 (0.36–0.98)*†	0.95 (0.43–0.98)*†‡	0.0004
H_{CDP}	0.75 (0.46–0.89)	0.79 (0.23–0.91)*	0.77 (0.68–0.89)	0.80 (0.2–0.9)*	0.8 (0.26–0.89)*‡	0.04
H_{RI-1}	0.53 (0.18–0.78)	0.64 (0.24–0.89)*	0.84 (0.7–0.96)*†	0.92 (0.61–0.98)*†	0.95 (0.64–0.99)*†‡	0.0001

for each consecutive ventilatory cycle (Fig. 1C). Each heart beat was therefore observed to be affected by vagal modulation differently according to its position in the ventilatory cycle. Because coupling caused these heart beat positions to be the same with consecutive breaths, we observed a heart rate time series in which the same pattern of RR interval fluctuation was repeated within each ventilatory cycle (Fig. 1D). This led to a small, discrete number of RR interval durations and hence banding of the RR time series.

Despite the apparently clear qualitative relationship between RR interval banding and pattern I coupling, the statistical correlation between our measure of cardioventilatory coupling (H_{RI-1}) and entropy measure derived from the RR time series plot (H_{rr}) approached, but did not achieve, statistical significance for the coupling pattern epochs (P=0.062) and no correlation was found for the 500-heart beat epochs (Table 1). Furthermore, there was no apparent difference in H_{rr} according to coupling pattern (Table 2).

RR interval consecutive difference time series

As with the raw RR time series, consecutive difference RR interval banding was significantly related to the presence of coupling and varied with specific coupling pattern. Banding was observed in 54% of pattern I epochs, diminished with other coupling patterns and occurred least (11%) in uncoupled epochs (Table 2). Referring to the pattern I example in Fig 1E, the RR interval consecutive difference time series shows two distinct bands, one (possibly two bands) ranging between 0 and 0.08 s and a second, narrower band at –0.1 s. In contrast, in Fig. 2E the RR interval consecutive difference time series for the uncoupled epoch shows an apparently random distribution of values between 0.05 and –0.05 s. As with the RR banding, the banding of the RR interval consecutive time series was found to correspond with repeating sequences of RR intervals (and hence RR interval consecutive differences) consequent upon the RR alignment to inspiratory onset.

We observed a significant correlation between H_{CD} and H_{RI-1} for both the coupling pattern and 500 heart beat epochs (Table 1). The H_{CD} values were lower during epochs of pattern I and II coupling than during patterns III and IV and uncoupled epochs (Table 2).

Consecutive difference phase portrait

Multiple complex patterns were observed in the consecutive difference phase portrait [(rr_n–rr_{n-1}) *vs* (rr_{n+1}–rr_n)]. The most commonly observed pattern was three discrete clusters of points (Fig. 1F) in various degrees of rotation. The observed clustering was significantly related to the presence of coupling and the specific coupling pattern. Clustering was observed in 62% of pattern I epochs, diminished with other coupling patterns and occurred least (11%) in uncoupled epochs. As with the other graphical plots, clustering was consistent with the stepwise RR interval and consecutive difference fluctuations. The number and distribution of clusters varied according to the pattern of RR interval variation during each ventilatory cycle and the point distribution expanded or contracted according to the degree of RSA. Where RSA was very low, little discrete clustering was observed within the small point distribution. Uncoupled epochs were associated with a central globular cluster or ring distribution; an example is shown in Fig. 2F.

H_{CDP} significantly correlated with H_{RI-1} (Table 1) and varied significantly with coupling pattern, being lowest during pattern I and III epochs (Table 2).

Modifying influences

A number of subjects, despite showing good evidence of coupling on the basis of the RI interval plot, failed to show any evidence of structure in the graphical RR time series plots. Conversely, banding or clustering was occasionally observed despite the absence of coupling. Epochs that were not consistent with the overall trend were therefore examined further. We were able to identify the following three factors that clearly altered the relationship between coupling and the qualitative appearance of structure and the associated quantitative measures.

Low RSA

Some subjects showed minimal heart rate variation due to RSA. RR and consecutive difference time series were therefore confined to a single narrow band and the consecutive difference phase portrait was confined to a small point distribution. Combined with the small degree of noise in these time series, this destroyed any definable structure within these plots despite the presence of coupling. Furthermore, at very low RR interval variation, the quantizing error of our 500 Hz sampling frequency became significant and an artefactual time series banding or clustering erroneously gave the appearance of structure when none existed. Although the low RSA and the quantizing effect were readily apparent from the graphical plots, in isolation the quantitative measures derived from these plots gave no clue as to their artefactual origin.

Heart rate/breathing frequency=2:1

For time series in which the heart rate/breathing frequency ratio approached 2:1, RR acceleration was followed by deceleration, and deceleration by acceleration. Despite the absence of coupling, this alternating pattern of HRV gave rise to a symmetrically double-banded appearance of the consecutive difference time series and a double cluster of points in its associated phase portrait. As with RSA, this error was readily apparent from the graphical plots.

Coupling pattern

The positioning of heart beats relative to inspiratory onset (and hence RSA) is different for different coupling patterns. Because the alignment of heart beats to the RSA is determined by the cardiac triggering, coupling patterns in which cardiac triggering occurs most commonly (patterns I, II and III) are associated with the most structured plots.

Discussion

In 1988 Babloyantz and Destexhe[10] described complex geometric patterns in the heart rate 'map of interval variation', i.e. a plot of the difference between two consecutive RR intervals plotted against the subsequent difference (equivalent to our RR interval consecutive difference phase portrait). Although not specifically associated with the phenomenon of cardioventilatory coupling, the structure was described as an 'unambiguous sign of the coherence in the interbeat interval' and the plotting method as 'useful for analysis of external factors influencing the sinus rhythm'. In 1999, we demonstrated that this structure could clearly be related to the phenomena of cardioventilatory coupling.[8]

A conspicuous feature of raw heart rate time series is the fast, respiratory phase-related modulation by RSA. With the onset of inspiration, vagal tone decreases to the sino-atrial pacemaker and a brief acceleration in heart rate ensues. During the expiratory phase, vagal tone returns and heart rate decreases.[6 7] The specific pattern of heart rate acceleration and deceleration which occurs with breathing is determined by the pattern of vagal modulation and the positioning of heart beats within the ventilatory phases. Because cardioventilatory coupling determines the timing of inspiratory onset it also determines the timing of vagal heart rate modulation by RSA. Furthermore, because the coupling interval (that between the initiating cardiac trigger and inspiratory onset) is fixed for a cardiac triggered breath at approximately 0.5 s,[1 4] heart beats tend to fall in fixed relationship with the waxing and waning pattern of vagal tone.[1 8 11] Because of this, the pattern of heart rate vagal modulation for the heart beats occurring during one breath will be similar to that in the following and each subsequent breath. In particular for pattern I coupling (constant entrainment and constant coupling interval), this HRV pattern repetition generally, although not invariably, causes a banded appearance in the RR interval time series and the RR interval consecutive difference time series, and the formation of discrete clusters within the RR consecutive difference phase portrait (Fig. 1).[8]

Because different coupling patterns vary in the degree to which they are cardiac-triggered, the best alignment between heart beats and the RSA curve (and hence the best correlation between coupling and geometric structure) is found for those coupling patterns associated with the greatest proportion of cardiac-triggered breaths. Thus phase portrait structure is seen best for pattern I, then patterns II and III, and least well for patterns IV and uncoupled.

Although we observed a statistical correlation between coupling and the entropy of the RR interval consecutive difference time series and its associated phase portrait, we could find no correlation with the entropy of the RR interval time series plot. There are at least two explanations for the improved correlation with the consecutive difference measures.

First, trends or non-stationarity in the heart rate time series are less apparent with consecutive difference measures. Thus, a trend in raw heart rate will tend to scatter RR intervals into varying histogram bins during the process of entropy measurement for H_{rr}. Consecutive difference measures ignore the absolute values of heart rate and measure only the beat-to-beat difference. Non-stationarity is therefore less of a problem in the calculation of H_{CD} and H_{CDP}.

Secondly the consecutive difference time series corresponds to a series of values that define the relationship between consecutive pairs of RR intervals, i.e. the relationship between two RR intervals or three heart beats. Each point on the phase portrait of the consecutive difference time series defines the relationship between three RR intervals or four heart beats. In contrast, RR interval time series plots display a series of single RR intervals or the relationship between two heart beats. In clinical epochs, heart rate/ventilation rate ratios of 3:1 and 4:1 are seen most commonly, and hence during coupling the repeating RR interval patterns are occurring over three or four RR intervals. Unlike the RR measures, therefore, the consecutive difference measures will tend to display the full structure of the pattern repetition.

In this paper we have demonstrated the presence of coupling without the need for a ventilatory signal. This is of potential value in many experimental protocols because, in contrast to the determination of the RR time series from the ECG, the determination of an inspiratory time series is technically difficult; inspiratory timing is prone to error and, unless care is taken, cardiac contamination of a ventilatory flow signal may lead to artefactual 'coupling'. The methods described for the demonstration of coupling in HR time series are understandably limited in the absence of RSA, as it is RSA that provides the displacement necessary to reveal the heart rate repetition, which in turn is the marker of coupling. If RSA is taken into account, cardioventilatory coupling may be added to the range of physiological processes that are revealed by beat-to-beat HRV analysis. Although generally applied to the influences of cardiac autonomic tone and the effect of respiration on heart rate, we have demonstrated that the heart rate time series is also capable of revealing the complex bidirectional interaction that exists between cardiac and respiratory frequency control.

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Volume kinetics of glucose solutions given by intravenous infusion[†]

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Glucose solutions given by intravenous (i.v.) infusion exert volume effects that are governed by the amount of fluid administered and also by the metabolism of the glucose. To understand better how the body handles glucose solutions, two volume kinetic models were developed in which consideration was given to the osmotic fluid shifts that accompany the metabolism of glucose. These models were fitted to data obtained when 21 volunteers who were given approximately 1 litre of glucose 2.5 or 5% or Ringer's solution (control) over 45 min. The maximum haemodilution was similar for all three fluids, but it decreased more rapidly when glucose had been infused. The volume of distribution for the infused glucose molecules was larger (~12 litres) than for the infused fluid, which amounted to (mean (SEM)) 3.7 (0.3) (glucose 2.5%), 2.8 (0.2) (glucose 5%), and 2.5 (0.2) litres (Ringer). Fluid accumulated in a remote (cellular) body fluid space when glucose had been administered (~0.2 and 0.4 litres, respectively), while expansion of an intermediate fluid space (7.1 (1.3) litres) could be demonstrated in 33% of the Ringer experiments. In conclusion, kinetic models were developed which consider the relationship between the glucose metabolism and the disposition of intravenous fluid. One of them, in which infused fluid expands two instead of three body fluid spaces, was successfully fitted to data on blood glucose and blood haemoglobin obtained during infusions of 2.5 and 5% glucose.

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Glucose solutions are frequently used to hydrate patients with acute disease or after surgery.[1 2] The volume changes in the body fluid compartments when infusing glucose solutions differ from those seen when infusing balanced electrolyte solutions in that transport of glucose into the cells causes osmotic transport of water. Later, the translocated water equilibrates with the extracellular fluid space as metabolism of glucose eliminates the osmotic pressure of the glucose molecule. This makes the volume effect of infused glucose solutions difficult to predict.

The purpose of the present report was to evaluate whether volume kinetic principles[3] can be used to study the disposition of the volume component of glucose solutions given by intravenous (i.v.) infusion. Volume kinetics has previously been used to analyse and simulate the effects of isotonic salt solutions in normo- and hypovolaemic volunteers[4–6] and also after surgery[7] and trauma.[8] These studies report the size of body volumes that become expanded and the rate at which fluid becomes distributed and eliminated. However, there was a need for a new kinetic model, which considers an additional volume located more peripherally. Successful application of such a model would make it possible to analyse the disposition of solutions that generate osmotic fluid shifts, which is what happens when glucose is taken up to the cells.

Materials and methods

Twenty-one healthy male volunteers, with no family history of diabetes, were included in two separate investigations.

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The first study comprised glucose 2.5% and the second glucose 5% and Ringer's acetate solution. The Local Ethics Committee approved both procedures and the informed consent of all subjects was obtained.

Glucose 2.5%

Twelve subjects aged between 24 and 36 (mean 28) yr of age and with a body weight of 62–113 (mean 79) kg participated. After an overnight fast, the volunteers rested comfortably on a bed for at least 20 min of equilibration before the experiments started at 08:00. Before any fluid was administered, a cubital vein of each arm was cannulated for the purpose of withdrawing (including sampling) blood and for infusing fluid, respectively. The volunteers were given an i.v. infusion of 12.5 ml kg^{-1} of glucose 2.5% with electrolytes (Na 70, Cl 45 and acetate 25 mmol $litre^{-1}$; Rehydrex, Pharmacia, Uppsala, Sweden) at a constant rate over 45 min via an infusion pump (Flo-Gard 6201, Baxter Healthcare Ltd, Deerfield, IL, USA). Venous blood was collected every 5 min for 75 min and thereafter every 10 min up to 195 min. The plasma glucose concentration was measured in single samples except for the baseline, which was in duplicate. The blood haemoglobin (Hb_b) concentration, the red blood cell count (RBC), and the mean corpuscular volume (MCV) were measured in duplicate samples, and the baseline in quadruplicate samples. The heart rate and arterial pressure were measured using an automatic device (Propaq 104, Protocol Systems Inc., Beaverton, OR, USA) immediately after each blood sampling procedure. Venous blood was also withdrawn at 0, 45, 125, and 195 min to determine the serum concentrations of sodium, potassium, and insulin.

The subjects voided just before the infusions started and, in the recumbent position, whenever necessary during the study. The urine volume and its concentration of glucose, sodium, and potassium were measured.

Glucose 5% and Ringer's acetate

Nine subjects (mean age 27 yr, range 24–38, and body weight 79 kg, range 59–88) underwent two i.v. infusion experiments on separate days at least 1 week apart. On one of these occasions they received 1000 ml of glucose 5% without electrolytes over 45 min via the infusion pump. The same amount of Ringer's acetate solution (Na 130, K 4, Ca 2, Mg 1, acetate 30, and Cl 110 mmol $litre^{-1}$) was given on the other occasion (Pharmacia). Blood was sampled every 5 min for 135 min to measure RBC, MCV, and the Hb_b and plasma glucose concentrations. Venous blood was also withdrawn at 0, 45, 75, and 135 min to measure the serum concentrations of sodium, potassium, and insulin. Monitoring of haemodynamics and urine was the same as in the study of glucose 2.5%.

Blood chemistry

The plasma glucose (P-glucose) concentration was measured with the GLU Gluco-quant reagent (Boehringer Mannheim) on a Hitachi 917 (Hitachi Co., Naka, Japan). The Hb_b concentration was measured on a Technicon H 2 (Bayer, Tarrytown, NY, USA) using colourimetry at 546 nm. RBC and MCV were measured with the same equipment, but by light dispersion at two angles using a helium neon laser. Before each infusion, one sample was drawn in duplicate or quadruplicate and the mean value was used in the calculations. The coefficients of variation for the samples were 1.2% for plasma glucose, 1.0% for Hb_b, 1.2% for RBC, and 0.5% for MCV. The serum concentration of insulin was determined by radioimmunoassay (Insulin RIA 100, Pharmacia) and the serum concentrations of sodium and potassium using an Ektachem 950IRC System (Johnson & Johnson, Inc., NY, USA).

Glucose kinetics

The volume of distribution for the glucose load (V_d) was used as the scaling factor between the P-glucose concentration and the amount of glucose that readily equilibrated with venous plasma. There is abundant evidence that the intracellular glucose belongs to another pool. First, the intracellular concentration of glucose is much lower than the extracellular concentration.[9] Second, glucose is rapidly phosphorylated when translocated into, for example, muscle cells.[10] Third, and probably most important, glucose requires an active transport mechanism to penetrate the cell membrane.[9]

To obtain V_d, the time–concentration profile of P-glucose for each glucose solution experiment was analysed according to a mono-exponential washout equation in which the plasma concentration (C) at any time (t) after a bolus injection of glucose is expressed as:

$$C = (C_0 - C_{baseline})e^{-kt} \qquad (1)$$

where k is the elimination rate constant, C_0 is the concentration when the elimination function is extrapolated back to t=0, and is the mean of the duplicate determinations of P-glucose just before the infusion started. During a constant-rate infusion, the equation used for the curve-fitting procedure was:[11]

$$C = (C_0 - C_{baseline})\ (1 - e^{-kt})\ /\ (kT) \qquad (2)$$

where T is the infusion time. After infusion, it was:

$$C = (C_0 - C_{baseline})\ [(e^{kt} - 1)\ /\ (kT)]e^{-kt} \qquad (3)$$

This model was fitted to the data using the Model-PK non-linear regression program for PC (McPherson Scientific, Rosanna, Australia). Weights inversely proportional to the predicted concentrations were applied. Further calculations included the area under the curve (AUC), which was obtained by the linear trapezoid method for the concentration–time profile of glucose in plasma. The clearance for the glucose load was obtained as the infused dose of glucose divided by the AUC and, in turn, the volume of distribution (V_d) as the clearance divided by k. The half-life ($T_{1/2}$) was obtained as the natural logarithm of 2 divided by k.

The following F test indicated whether it was statistically justified to fit the data to an equation that contained one more exponent (n+1) than the simpler equation (n):[12]

$$F = [(SSQ_n - SSQ_{n+1}) / SSQ_{n+1}] \times [df_{n+1} / (df_n - df_{n+1})] \quad (4)$$

where df is the degrees of freedom and SSQ is the sum of squares for the difference between the measured dilution of the plasma and the optimal curve fit. A high F value makes it more likely that the curve is best described by the more complicated model, and significance testing is done by consulting a standard statistical table.

According to Equation 4, the one-compartment open model was consistently justified for analysing the kinetics of the infused glucose load. As glucose is a small molecule, which easily diffuses across the plasma membrane[13] but requires active transport to enter the cells, a decreasing amount of glucose in V_d corresponds to the uptake of glucose into a peripheral compartment, which does not equilibrate with venous plasma. Hence, the net uptake of glucose into this remote compartment was calculated for each interval between the earlier (time 1) and the later (time 2) sampling point. During infusion, it was obtained as:

$$\text{Uptake of glucose} = \text{infused glucose} - V_d\,(\text{P-glucose}_2 - \text{P-glucose}_1) \quad (5)$$

After infusion, it was:

$$\text{Uptake of glucose} = V_d\,(\text{P-glucose}_1 - \text{P-glucose}_2) \quad (6)$$

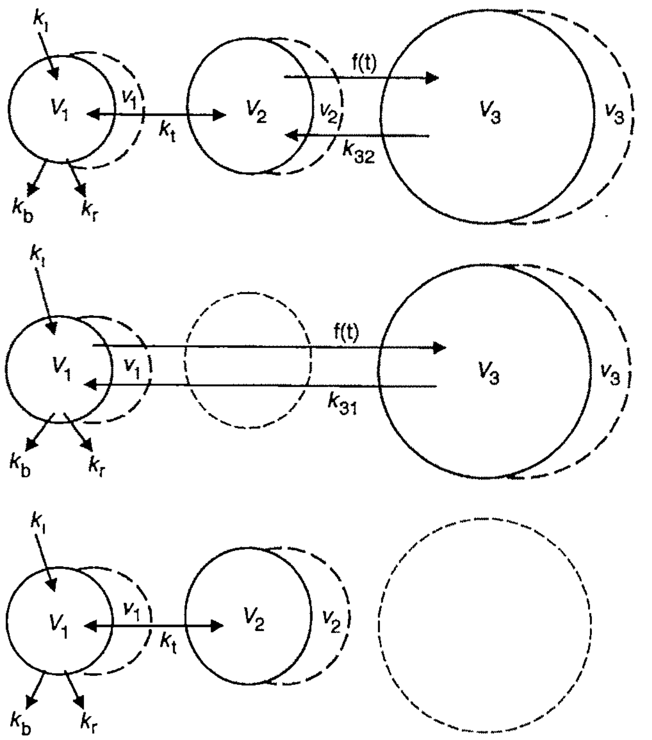

Fig 1 The model used to analyse the volume kinetics when an osmotic gradient acts like a driving force, $f(t)$, in the distribution of infused fluid (top). When glucose 2.5 and 5% were infused, expansion of V_2 did not become statistically significant, and water then entered V_3 in proportion to the insulin-dependent uptake of glucose to the cells (middle). Ringer's solution does not induce any marked osmotic fluid shift and, therefore, expands only one or two body fluid spaces, which communicate freely at a rate governed by a constant k_t (bottom). The elimination of fluid is given by basal fluid losses, k_b, and a renal mechanism which operates at a rate given by the product of k_r and the dilution of V_1.

Volume kinetic models

In the model for kinetic analysis of the distribution and elimination of infused fluids (Fig. 1, upper), an i.v. infusion is given at a constant rate (k_i) and enters a central body fluid space having the volume (v_1). The volume (v_1) strives to be maintained at the baseline volume V_1 by allowing fluid to leave the space at a controlled rate proportional by a constant k_r to the deviation of v_1 from the target volume V_1 (this may be considered as dilution-dependent urinary excretion) and at a basal rate (k_b, perspiration and baseline diuresis, fixed rate). The net rate of fluid exchange between v_1 and v_2 is considered to occur at a rate proportional to the relative difference in deviation from the target values (V_1 and V_2) by a constant (k_t).

Osmotic shifts of fluid, if present, take place between V_2 and a more remote fluid space, V_3, and has the strength $f(t)$. As all infused fluids were isotonic, the net transfer of water from v_2 to v_3 occurred at a rate governed directly by the osmotic pressure of glucose; 3.6 ml of water was translocated to v_3 per millimole of glucose taken up by V_3. As water must accompany glucose in order to maintain equal osmolality inside and outside V_3, the factor 3.6 was obtained from the osmolality of glucose when being in an isotonic solution; 1 litre contains 50 g of glucose, which is equal to 278 mmol, and each mmol is then capable of bringing along 1000 ml/278 mmol=3.6 ml of water. In the model, fluid also returns from v_3 to v_2, which occurs at a rate proportional by a constant (k_{32}) to the dilution of V_3.

Furthermore, V_2 was only reported if it was statistically justified by comparing a bi-exponential and tri-exponential curve by means of the F test (Equation 4). If V_2 was not statistically justified, the constant governing the diffusion of fluid from V_3 to V_1 was called k_{31} (Fig. 1, middle).

In order for the kinetic program to calculate the net balance of fluid between V_1 and V_3 (Fig. 1, lower), it required a starting estimate for V_3. This was set at 40% of the body weight.[4] The accumulation and elimination (k_{31}) of

Table 1 Results of pharmacokinetic analysis of the infused glucose molecules (top) and volume kinetic analysis of the accompanying fluid volume (below) when approximately 1 litre of iso-osmotic glucose 2.5% (left column) or glucose 5% (right column) solution was infused over 45 min in male volunteers. The first line for each parameter gives the mean (SEM) of all estimates in the respective group. The second line shows the precision of these estimates, specified as the mean (SEM) of the standard errors (SE) associated with them. [a]Because of skewed distribution, these results are given as the median and 25th and 75th percentiles

	Glucose 2.5% (n=12)	Glucose 5% (n=9)
Glucose kinetics		
C_0 (mmol litre^{-1})	11.8 (0.6)	24.4 (0.9)
SE	0.7 (0.1)	1.3 (0.1)
k (10^{-3} min^{-1})	61 (5)	49 (5)
SE	4 (1)	3 (1)
V_d (litre)	12.3 (0.9)	11.5 (0.4)
$T_{1/2}$ (min)	12.1 (1.3)	15.7 (2.2)
Clearance (ml min^{-1})	0.72 (0.05)	0.54 (0.04)
Sum of squares	0.48 (0.13)	1.46 (0.43)
Volume kinetics		
V_1 (litre)	3.68 (0.31)	2.70 (0.22)
SE	0.47 (0.07)	0.24 (0.03)
k_r (ml min^{-1})	66 (51,134)[a]	32 (16)
SE	16 (12,32)[a]	7 (1)
k_{31}/V_3 (ml min^{-1})	2.1 (0.1,5.2)[a]	2.6 (1.8,3.0)[a]
SE	1.6 (1.4,4.9)[a]	0.7 (0.4,0.9)[a]
Sum of squares	0.075 (0.010)	0.100 (0.026)

fluid in V_3 could then be calculated and was presented as k_{31}/V_3 (Table 1), that is slope for the dilution of V_3.

$f(t)$ was set to zero in the infusions of Ringer's acetate as the changes in blood glucose were very small. Here, both a one-volume and a two-volume model were fitted to the data on dilution (Fig. 1, lower), and the F test was again used to select the optimal one for presentation. The mathematical details involving $f(t)$=0 have been given in previous work[3 5] while those for $f(t)$>0 are given in the Appendix.

Calculations

Volume kinetics

The dilution of the plasma in the cubital vein was used to quantitate the water load. As the sampled plasma is a part of V, we obtain:

$$(v(t) - V) / V = [\text{baseline Hb}_b / \text{Hb}_b(t) - 1\ ] / (1 - \text{baseline haematocrit}) \qquad (7)$$

at any time (t). The dilution of the RBC count was calculated in the same way as for Hb_b and the mean value of the two was used, after correction for changes in cell volume as indicated by MCV. Furthermore, a correction was always made for the losses of erythrocytes in connection with the blood sampling procedure based on the baseline blood volume as estimated according to a regression formula based on the height and weight of subjects.[14] A k_b of 0.8 ml min^{-1} was used, which represents the sum of the insensible fluid loss of 10 ml kg^{-1} day^{-1} (0.5 ml min^{-1})[15] and the withdrawn amount of extracellular fluid during blood sampling.

The model parameters were calculated on a computer using Matlab version 4.2 (Math Works Inc., Natick, MA, USA), in which a non-linear least-squares regression routine based on a modified Gauss–Newton method was used. Weights inversely proportional to the predicted dilution+0.1 were applied. The factor 0.1 was added to the denominator to avoid division by zero at baseline.

Sodium dilution method

The diffusion of fluid into the intracellular space was also estimated from a comparison between the distribution volume corresponding to the dilution of the serum sodium level and the actual amount of infused fluid and the urinary excretion of water and sodium.[16 17] More details about the calculations are given in the Appendix.

Statistics

The results are expressed as the mean and the standard error of the mean (SEM). Differences between the experiments were evaluated by analysis of variance (ANOVA). Correlations between parameters were studied by simple and multiple linear regression; P<0.05 was considered significant.

Results

The Hb_b concentration decreased progressively during the glucose infusions but returned to baseline approximately 45 min after they were completed. Ringer's solution was, however, followed by a more persistent reduction in Hb_b (Fig. 2, top).

The plasma glucose and serum insulin concentrations increased in response to glucose 2.5 and 5%, whereas a slight reduction of them occurred during the infusion of Ringer's solution (Fig. 2, middle and lower). Glucose 5% induced mild hypoglycaemia; the mean plasma glucose level from 60 min after the infusion ended and onwards was below the normal range (3.6 mmol litre^{-1}) in six of nine infusions of glucose 5% (lowest 2.7 mmol litre^{-1}). In contrast, hypoglycaemia did not occur after any of the other infusion experiments (P<0.01 *vs* glucose 2.5%).

Plots of the dilution of venous plasma, with a correction for blood sampling, showed that dilution resulting from the three solutions had a similar time course (Fig. 3). Some of the volunteers receiving glucose showed a negative dilution at the end of the experiment.

Glucose kinetics

The volume of distribution for the administered glucose molecules was 12.3 and 11.5 litres, respectively, when glucose 2.5 and 5% were infused (Table 1, upper). The corresponding half-lives for the glucose loads were 12.1 and 15.7 min (non-significant differences). The AUC for plasma

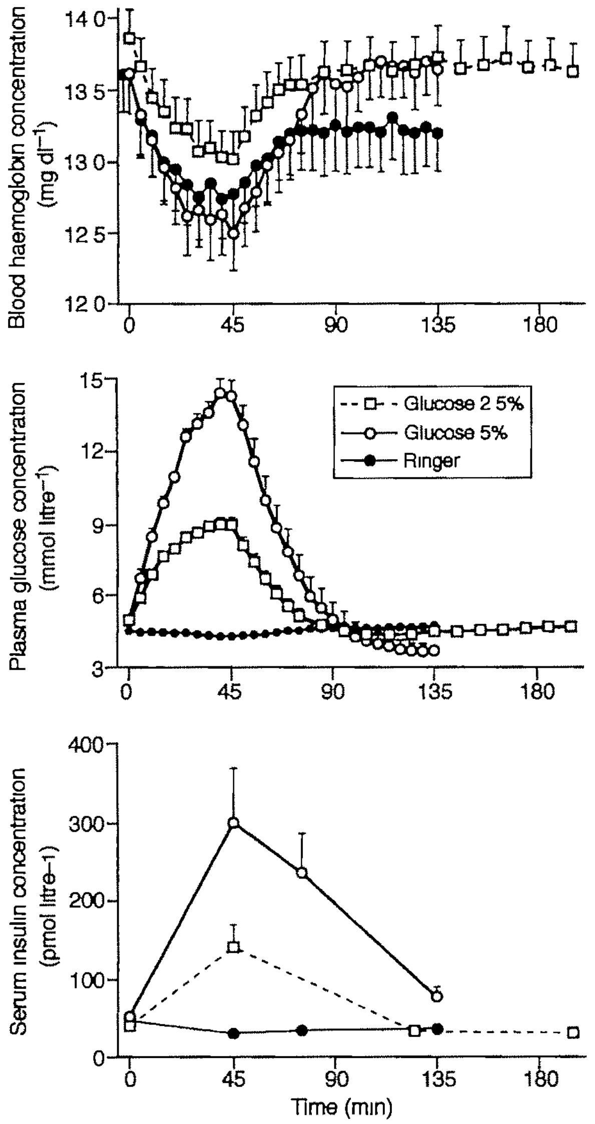

Fig 2 The blood haemoglobin (top), plasma glucose (middle) and serum insulin (bottom) concentrations during and after a 45-min i v infusion of approximately 1 litre of glucose 2.5%, glucose 5%, and Ringer's acetate solution in healthy male volunteers.

glucose correlated strongest with the serum insulin concentration measured at 125–135 min (r=0.82, P<0.001).

The calculated uptake of glucose into V_3 increased progressively during the infusions, but it had returned to baseline 90 min after they were completed (Fig. 4). The calculated uptake of glucose for each time interval was then entered as the driving force for fluid uptake (3.6 ml mmol^{-1} glucose) into V_3 in the subsequent kinetic analysis.

Volume kinetics

In the case of glucose infusions, the two-volume kinetic model yielded relatively good curve fits, which were not improved by assuming that the infused fluid also expanded an intermediate body fluid space. The curve fits were relatively good also for the subjects who were given glucose 2.5% and who showed the highest inter-subject variability, as evidenced by Figure 5 and also by the modest standard errors for the parameter estimates (Table 1, lower). The three-volume model was either not statistically significant or the program did not converge to yield meaningful estimates. Therefore, the two-volume model was chosen for presentation.

The mean size of V_1 was 3.68 litres for the infusions of glucose 2.5% and 2.70 litres for glucose 5% (ANOVA, P=0.03). The elimination rate constant k_r differed more between the glucose experiments, the estimates being 77 and 32 ml min^{-1}, respectively (P<0.07; Table 1, lower). The estimates of k_{31}/V_3 varied more between the volunteers than the other parameters, and one volunteer who became haemoconcentrated after glucose 2.5% even showed a clearly negative k_{31}/V_3 (third patient in the top row of Fig. 5). There was no significant difference between the groups with respect to k_{31}/V_3.

The two-volume model was statistically justified in six of the experiments with Ringer's acetate solution. The sizes of V_1 and V_2 were 2.39 and 7.12 litres, respectively (Table 2). The remaining three volunteers, who handled Ringer's solution according to the one-volume model, had rates of

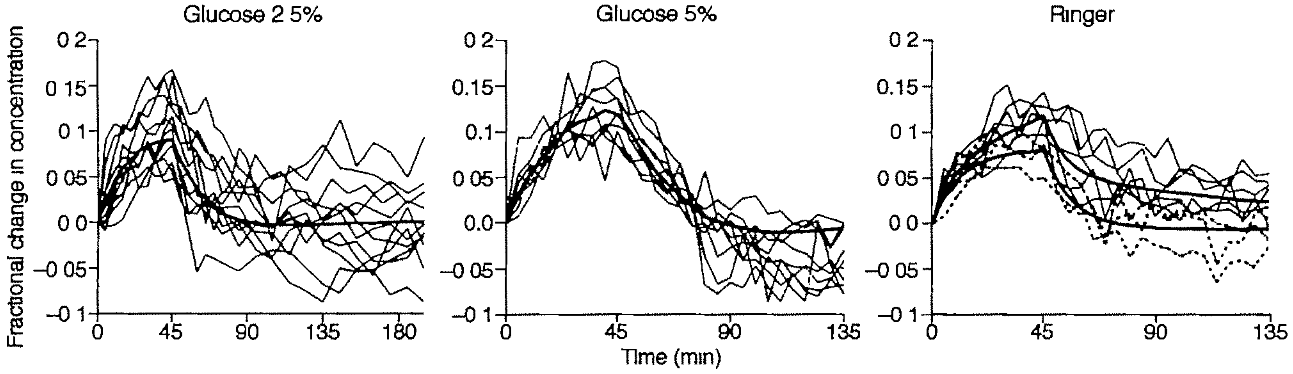

Fig 3 Dilution–time curves for individual volunteer experiments (fine lines) and a simulated curve based on the mean values for the parameter estimates obtained in the volume kinetic analysis of these experiments (thick lines). Two modelled curves are shown for Ringer's acetate (right figure) as the two-volume model was statistically justified in six of the nine experiments (upper thick line) and the one-volume model in the others (lower thick line), the latter being based on experiments illustrated by irregular fine lines.

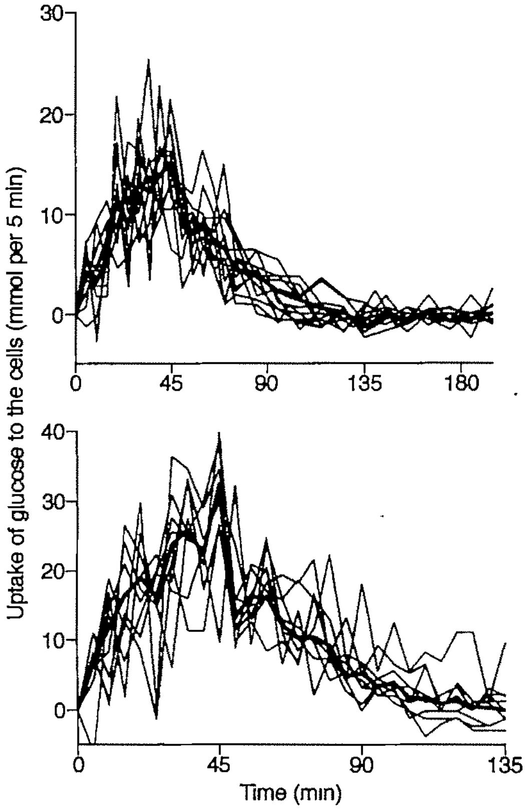

Fig 4 Calculated uptake of glucose into the cells during and after infusion of glucose 2.5% (upper) and glucose 5% (lower) for individual volunteer experiments (fine lines) and as the mean for the group (thick line).

fluid elimination, expressed as k_r/V_1, nearly three times higher than the others (0.092 *vs* 0.032 min^{-1}; $P<0.03$).

Comparisons between the infusions

Plots based on the average parameter estimates were used to describe the body's handling of the infused fluids. The maximum dilution of V_1 was similar for all infusions, but it decreased more rapidly when glucose had been infused (Fig. 6, top). The trend was the same when the dilution–time curves were converted into volume–time plots by multiplying the function $(v_1(t) - V_1)/V_1$ by the estimate of V_1 to obtain $v_1(t) - V_1$ (Fig. 6, middle). The modelled volume change in the most remote fluid space, which was V_3 for glucose and V_2 for Ringer's, was most pronounced and long lasting for glucose 5% (Fig. 6, bottom).

Haemodynamics, sodium dilution, and urinary excretion

There were no significant changes in systolic and diastolic arterial pressure during the experiments. The heart rate increased significantly from 90 min and onwards during the experiments with glucose 5% (66.9 (2.7) *vs* 62.9 (2.4) beats min^{-1} during infusion, $P<0.001$). No corresponding change occurred after administration of glucose 2.5% (62.2 (1.3) *vs* 63.7 (1.4) beats min^{-1} during infusion).

The calculations of fluid shifts, based on the dilution of the serum sodium concentration, indicated the existence of a slight cellular accumulation of fluid at the end of the experiments with glucose 5% (Table 3). This fluid induced a smaller urinary loss of sodium and potassium than the other ones, while the volume of urine was larger in response to both glucose solutions than to Ringer's acetate.

Three of the volunteers who received glucose 5% had traces of glucose in their urine. The excreted glucose amounted to 5, 5, and 10 mmol (total amount infused 278 mmol). No glucose could be recovered from the urine when the other solutions were infused.

Discussion

Glucose solutions are not used as volume expanders, but they certainly exert volume effects in the body. The present study shows that the volume effect during infusion of isotonic glucose 2.5 and 5% solutions, as indicated by the acute haemodilution, is very close to that recorded for Ringer's solution. Further studies on the dilution–time curves were made by applying volume kinetic models to the data. In contrast to Ringer's solution, the kinetics of the glucose solutions needed to be analysed by taking into account the body's handling of a glucose load and the effects on water distribution exerted by the osmotic pressure of infused glucose. These results indicate that glucose solution expands a quite small functional body fluid space. The size of V_1 was close to the expected size of the plasma volume and, for many subjects given glucose 5% in sterile water, it was even smaller. Furthermore, we found no evidence that the infused fluid expanded a body fluid space between V_1 and V_3, as is often the case with Ringer's solution.[4–6] Consequently, no results are reported according to the three-volume model. The fluid that entered V_3 must have travelled through such a body fluid space (V_2) but apparently without expanding it to any significant degree. This might be the case in volume kinetics provided that the inflow and outflow of fluid to V_2 are roughly in balance.

The kinetic analysis further indicates that some of the infused fluid remained in the cells at the very end of the experiments when glucose 5% had been given. This view receives support from the sodium-based calculations of the net fluid over the cell membrane.[15] [16] The fact that 25 mmol of sodium was lost by urinary excretion, while no sodium was infused, might account for some of the cell accumulation of fluid. Furthermore, a fraction of the glucose might have been stored as glycogen, a process augmented by high insulin concentrations, before being metabolized into carbon dioxide and water. The fluid remaining in the cells might serve to explain why the total measured urinary excretion was smaller in response to glucose 5% than to

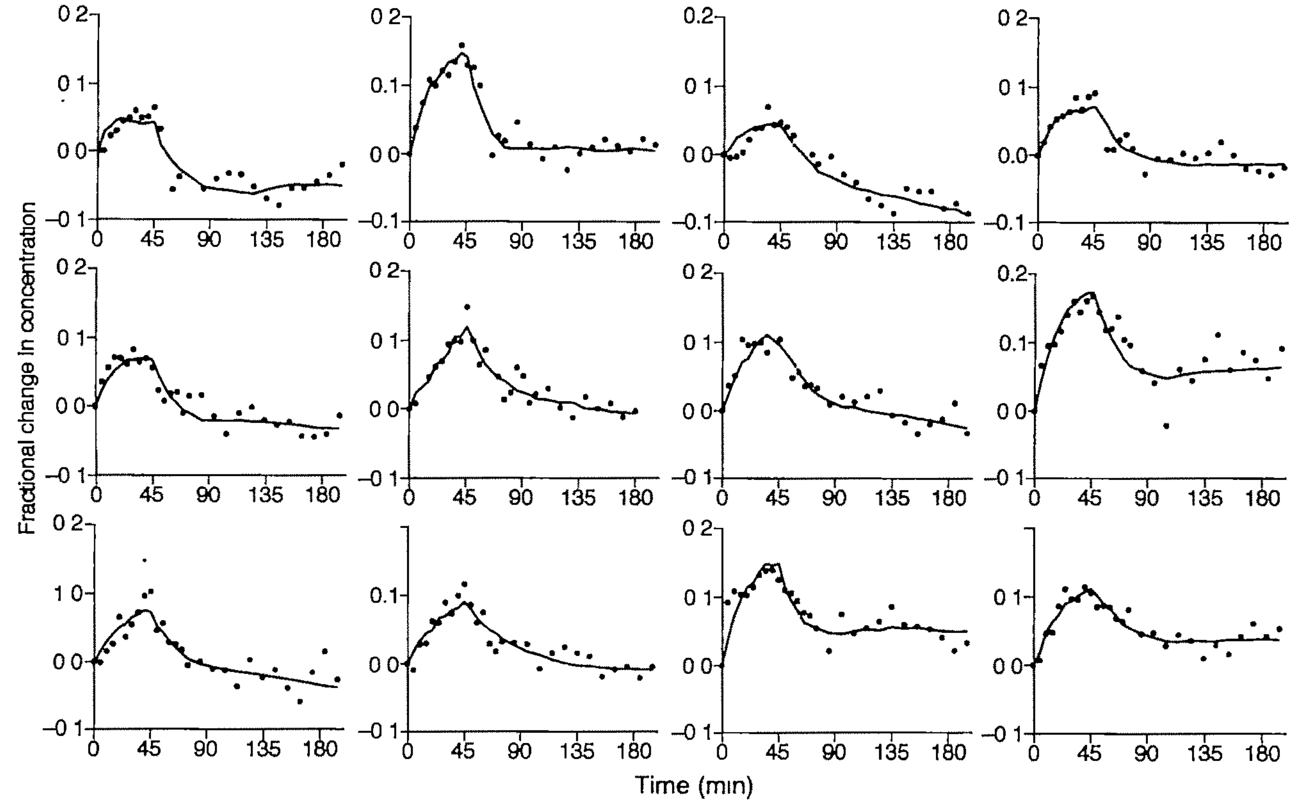

Fig 5 The fractional dilution of venous plasma in 12 experiments when 12 5 ml kg^{-1} of glucose 2.5% was given by i v. infusion to male volunteers over 45 min (dots) and the curve fits resulting from the subsequent volume kinetic analysis (fine lines).

glucose 2.5%. The urinary excretion after infusion of Ringer's acetate was, however, only half as large as after the glucose infusions.

In our volunteers, the strong insulin response even promoted slight hypoglycaemia and hypovolaemia and probably also physical stress, as the heart rate increased only at the end of the experiments with glucose 5%. These adverse effects suggest that a lower infusion rate of glucose 5% should be recommended than the one we used in the present study. A similar post-infusion 'rebound hypoglycaemia' has been reported after sudden withdrawal of total parenteral nutrition,[1] and also in newborns after glucose solution has been given at a high rate to their mothers just before delivery by Caesarean section.[19 20]

The slight glucosuria that occurred in some of the experiments with glucose 5% might have reduced k_{31}, as the kinetic models handle such events as if the infused glucose enters the cells while the accompanying fluid never returns to V_1. Simulations showed that the impact of the glucosuria was small, however; the 'lost' glucose only constituted 3.6% of the infused amount in the most pronounced case. Another uncertainty is how precise the kinetic models are when the dilution is negative. In such cases, we set the dilution-dependent elimination of fluid to zero, although dilution-dependent mechanisms for the generation of urine probably operate with a delay and do not 'shut off' as soon as zero dilution is reached. Hence, the measured urinary excretion during the period of hypovolaemia sometimes exceeded the volume indicated by k_b alone.

Table 2 Volume kinetic data for i v. infusions of 12 5 ml kg^{-1} of Ringer's solution over 45 min in nine male volunteers The results are reported according to whether the one-volume or the two-volume model was statistically justified The data are the means (SEM). The first line for each parameter gives the estimate and the second line shows the standard error (SE) associated with this estimate

Parameter	**Estimate**
One-volume model	
n	3
V (litre)	2.84 (0.16)
SE	0.81 (0.29)
k_r (ml min^{-1})	282 (39)
SE	35 (13)
Sum of squares (10^{-3})	0 092 (0.032)
Two-volume model	
n	6
V_1 (litre)	2.39 (0 26)
SE	0.53 (0 12)
V_2 (litre)	7 12 (1.25)
SE	1 38 (0.27)
k_t (ml min^{-1})	173 (27)
SE	48 (11)
k_r (ml min^{-1})	62 (16)
SE	16 (3)
Sum of squares (10^{-3})	0 031 (0 004)

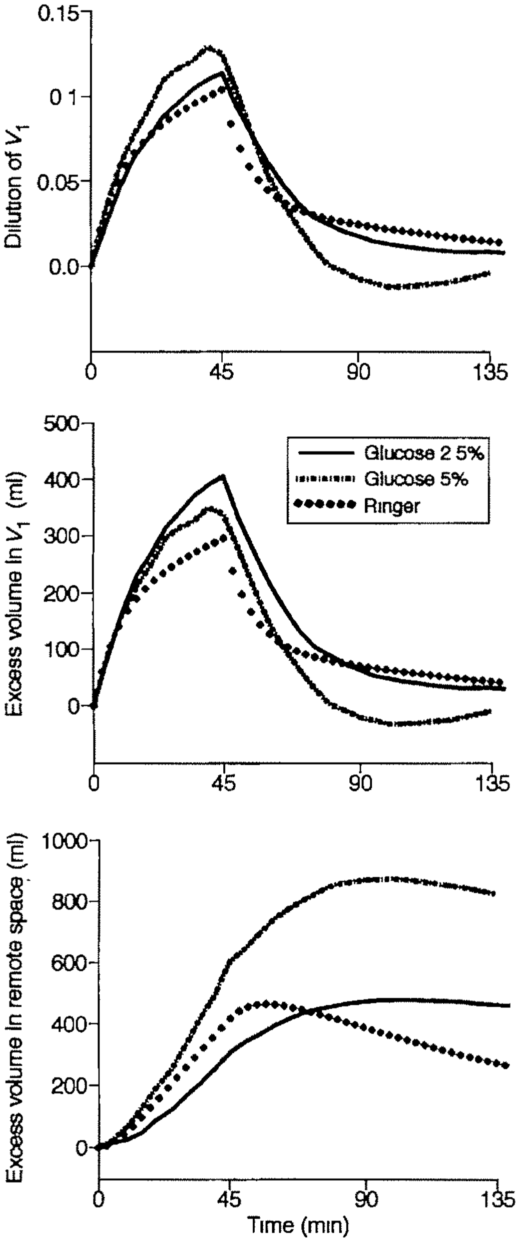

Fig 6 Simulations of the dilution of V_1 (top), the volume change of V_1 (middle), and the volume change of the most remote body fluid space, V_2 or V_3 (bottom), when about 1 litre of glucose 2.5%, glucose 5%, and Ringer's acetate solution are infused at a constant rate over 45 min. The curves were based on the mean values obtained in the volume kinetic analyses shown in Tables 1 and 2. For Ringer's acetate, however, the simulated curve is the weighted mean for the three experiments analysed by the one-volume model and the six analysed by the two-volume model, that is dilution (t) = (3 × one-volume curve (t)+6 × two-volume curve (t))/9.

Table 3 Calculated accumulation of fluid in the cells at the end of each experiment and the measured urinary excretion of fluid, sodium, and potassium (mean (SEM)) [a]The change in intracellular fluid (ΔICF) volume was indicated by the serum sodium method

	Glucose 2.5%	**Glucose 5%**	**Ringer's acetate**	ANOVA
ΔICF (ml)[a]	60 (70)	218 (86)	−100 (40)	$P<0.01$
Urine volume (ml)	1022 (145)	841 (118)	472 (96)	$P<0.01$
Urinary sodium (mmol)	63 (11)	25 (3)	51 (11)	$P<0.04$
Urinary potassium (mmol)	26 (3)	9 (2)	15 (2)	$P<0.001$

The derived volume kinetic models may be used to understand the relationship between the disposition of fluid given i.v. and the glucose metabolism. We hope that there will be a useful asset in studies of fluid balance during and after surgery, such as when evaluating the effects of surgery-induced insulin resistance on the disposition of infused fluid. When both the glucose kinetics and the volume kinetics have been analysed, a simulation program can predict, for example, the effect of a reduction in the glucose clearance on the disposition of infused fluid. Such programs have been constructed. Before they are used, however, more volunteer experiments are needed to outline how much k_r and k_{31} normally change at different infusion rates and glucose concentrations, as these parameters varied much more than the size of V_1 in the present study. The volume kinetic parameters have previously been found to be quite similar when Ringer's acetate is given at different infusion rates.[4 18]

The kinetic models derived here are also valid for other fluids, which induce a fluid shift to or from V_3 as a result of osmotic forces, such as hypertonic saline with and without dextran added. Their usefulness is not changed by the fact that glucose and hypertonic solutions shift fluid in opposite directions. In the case of hypertonic saline, calculating $f(t)$ is easy as it can be deduced directly from the infused amount of sodium.

In conclusion, kinetic models showing the relationships between the disposition of infused fluid and the glucose metabolism were developed and successfully applied to data from volunteers. Glucose 2.5 and 5% expanded a functional body fluid space of similar size as the plasma volume when account had been taken of the fluid shifts associated with the metabolism of glucose.

Appendix

Volume kinetics

When glucose is infused, uptake of glucose into the cells (V_3) is followed by a fluid shift in proportion to the change in osmolality across the cell membrane, $f(t)$. In cases where an intermediate body fluid space between V_1 and V_3 is not statistically significant, the differential equations showing the changes in volumes v_1 and v_3, respectively, are:

$$\begin{cases} \dfrac{\mathrm{d}v_1}{\mathrm{d}t} = k_i - k_b - k_r\dfrac{v_1 - V_1}{V_1} - f(t) + k_{31}\dfrac{v_3 - V_3}{V_3}, \quad v_1(0) = V_1 \\ \dfrac{\mathrm{d}v_3}{\mathrm{d}t} = f(t) - k_{31}\dfrac{v_3 - V_3}{V_3}, \quad v_3(0) = V_3 \end{cases} \tag{8}$$

Introduce

$$w_1 = \frac{v_1 - V_1}{V_1}, \; w_2 = \frac{v_3 - V_3}{V_3}$$

and we obtain:

$$\begin{cases} \dfrac{dw_1}{dt} = \dfrac{k_i - k_b}{V_1} - \dfrac{k_r}{V_1} w_1 - \dfrac{1}{V_1} f(t) + \dfrac{k_{31}}{V_1} w_2 \\ \dfrac{dw_2}{dt} = \dfrac{1}{V_3} f(t) - \dfrac{k_{31}}{V_3} w_2 \end{cases} \tag{9}$$

These differential equations cover the volume kinetics model in the following three cases, infusion (k_i>0), no infusion (k_i=0), and w_1<0, in which case k_r=0. The initial values of the process are $w_1(0)$=0 and $w_2(0)$=0. At time t=T_1, the infusion stops, and the solution then has the values $w_1(T_1)$=w_{1T1} and $w_2(T_1)$=w_{2T1}. We continue with these values as initial values and k_i=0. If, at time t=T_2, $w_1(T_2)$=0 and dw_1/dt (T_2)<0, we set k_r=0 and continue the solution of (2) with the initial values $w_1(T_2)$=0, $w_2(T_2)$=w_{2T2}

Introduce vector and matrix notation:

$$\overline{w}\begin{pmatrix} w_1 \\ w_2 \end{pmatrix}, \quad A = \begin{pmatrix} -(k_r/V_1) & (k_{31}/V_1) \\ 0 & (k_{31}/V_3 \end{pmatrix},$$

$$\overline{a}(t) = \begin{pmatrix} (k_i - k_b/V_1) - (f(t)/V_1) \\ (f(t)/V_3) \end{pmatrix} \tag{10}$$

The differential equations in Equation 9 can be written as:

$$\frac{d\overline{w}}{dt} = A\overline{w} + \overline{a}(t) \tag{11}$$

The solution of this linear system of differential equations is:

$$\overline{w}(t) = e^{A(t-T)}\overline{w}(T) + \int_T^t e^{A(t-s)}\overline{a}(s)\,ds \tag{12}$$

where e^{At} is the exponential matrix, T is the initial time, and $\overline{w}(T)$ the corresponding initial value. The integral can be evaluated if $\overline{a}(t)$ is approximated by a constant $\overline{a}_k$ in the time interval $[t_k, t_{k+1}]$. The numerical solution $\overline{w}_{k+1}$ at t=t_{k+1} is then computed recursively from

$$\overline{w}_{k+1} = e^{A\Delta t}\overline{w}_k + (e^{A\Delta t} - I)A^{-1}\overline{a}_k, \quad k = 0, 1, \ldots, N-1 \tag{13}$$

where $\Delta t = t_{k+1} - t_k, \overline{w}_0 = \overline{w}(T)$ and provided that A is non-singular. In cases where k_r=0, however, A is singular and the recursion formula (Equation 13) cannot be used. Instead, we use

$$\overline{w}_{k+1} = e^{A\Delta t}\overline{w}_k + [\Delta t(I + \alpha A) - \alpha^2(1 - e^{-\Delta t/\alpha})A]\overline{a}_k \tag{14}$$

where α=V_3/k_{31}.

The *three-volume model* is described by Equation 9 with

$$\overline{w} = \begin{pmatrix} w_1 \\ w_2 \\ w_3 \end{pmatrix},$$

$$A = \begin{pmatrix} (-k_r/V_1) - (k_t/V_1) & (k_t/V_1) & 0 \\ (k_2/V_2) & -(k_t/V_2) & (k_{32}/V_2) \\ 0 & 0 & (-k_{32}/V_3) \end{pmatrix},$$

$$\overline{a}(t) = \begin{pmatrix} (k_i - k_b)/V_1 \\ (-f(t)/V_2) \\ (f(t)/V_3) \end{pmatrix} \tag{15}$$

The solution is given by Equation 12, and after approximating $\overline{a}(t)$ with piecewise constant values as in the two-volume model, the numerical solution is obtained from Equation 13; the matrix A is non-singular also in the special case k_r=0.

Sodium dilution method

As sodium ions (Na) are distributed throughout the extracellular fluid (ECF) space, the serum sodium concentration at any time (t) during or after i.v. infusion of fluid (S-Na$_t$) equals the amount of Na in the ECF volume divided by the current ECF volume. This relationship can be expressed as:

$$\mathrm{S-Na_t} = \frac{\text{Added Na} + (\mathrm{S-Na_o} \times \mathrm{ECF_o} - \mathrm{Na_{loss}})}{(\mathrm{ECF_o} + \text{infused volume} - \text{urine volume} - \Delta\mathrm{ICF})} \tag{16}$$

where S-Na$_o$ and ECF$_o$ are the serum sodium concentration and ECF volume at baseline, respectively, Na$_{loss}$ is the natriuresis (in mmol), and ΔICF is the change in the water content of the intracellular fluid compartment. AS ECF$_o$ corresponds to 20% of the body weight,[8] ΔICF could be calculated by rearranging Equation 16:

$$\Delta\mathrm{ICF} = \mathrm{ECF_o} + (\text{infused} - \text{urine})\text{volume} - \frac{\text{Added Na} + (\mathrm{S-Na_o} \times \mathrm{ECF_o} - \mathrm{Na_{loss}})}{\mathrm{S-Na_t}} \tag{17}$$

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Heparin pretreatment does not alter heparin requirements during cardiopulmonary bypass

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Heparin infusion may cause heparin resistance and may affect monitoring by measurement of the activated coagulation time (ACT), making the assessment of anticoagulation difficult, with the risk of over- or undertreatment, especially during cardiac surgery. We studied two groups of patients undergoing cardiopulmonary bypass (CPB): patients on heparin infusions (group H) and heparin-naive controls (group C). All patients received heparin 300 IU kg^{-1} before CPB and a further dose of 5000 IU if the ACT 5 min after commencing bypass was less than 400 s. Measurements of ACT, heparin concentration, antithrombin-3, thrombin–antithrombin complex, prothrombin fragment F_{1+2} and D-dimers were made before and 5 and 20 min after start of CPB. A second dose of heparin was given to eight out of 18 patients in group C and 10 out of 24 in group H. Antithrombin-3 in group H was significantly less than in group C at 5 min [59 (14) *vs* 52 (9)%, $P<0.05$]. ACT was significantly lower in group H than group C at 20 min [387 (64) *vs* 431 (67) s, $P<0.05$]. Despite ACTs of less than 400 s in both groups, no coagulation was seen, suggesting that 300 IU kg^{-1} heparin is a safe dose for anticoagulation in CPB even after heparin therapy.

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Keywords: blood, anticoagulants, heparin; blood, antithrombin; surgery, cardiovascular

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In addition to the large variation in patient response to heparin,[1] some patients who receive an i.v. infusion of heparin need large doses of heparin to achieve anticoagulation.[2 3] This is often termed 'heparin resistance'. The precise mechanism of this heparin resistance is still unknown; it could be caused by a decrease in antithrombin (AT-3) concentration during heparin infusion.[3–5] Release of platelet factor 4 can also cause heparin resistance.[6–8]

Patients with unstable angina are commonly managed with i.v. heparin therapy and often present for urgent coronary revascularization. In such patients, the management of their anticoagulation for cardiopulmonary bypass (CPB) can be difficult. The AT-3 concentration can be increased either by giving fresh frozen plasma or AT-3 concentrate[3 9] or more heparin can be given until an acceptable degree of anticoagulation is achieved.[5 7 10] The former is expensive and time-consuming. The latter method, which is the more usual clinical approach, is difficult to monitor, and patients given greater doses of heparin have a greater risk of postoperative bleeding and blood transfusion.[9 11] It is uncertain what constitutes adequate anticoagulation in these patients.

In our department we monitor heparinization peroperatively with activated coagulation time (ACT) and we obtain an ACT of 400 s or greater for CPB. However, we accept a lower ACT in patients who show marked heparin resistance (i.e. failure to obtain clinically adequate ACT despite apparently sufficient heparin).

We assessed heparin resistance in our patients, the relationship between this and indices of coagulation and anticoagulation, and verified that accepting a lower ACT did not increase subclinical coagulation or harm the patient. We feel this will clarify the management of this patient group and prevent the potential complications and disadvantages associated with further doses of heparin or the use of fresh frozen plasma or AT-3 concentrate.

Methods

We studied patients undergoing coronary artery graft surgery over a 9-month period. Group H had received an i.v. heparin infusion for unstable angina for more than 72 h before surgery. Group C were selected as a control group, as the next suitable patient on the operating list after a patient

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Table 1 Patient characteristics. Mean (range) or mean (SD) No significant differences between groups

	Control group (n=18)	Heparin infusion group (n=24)
Age (yr)	59 (44–73)	60 (39–75)
Height (cm)	171 (11)	171 (9)
Weight (kg)	81 (14.1)	76.4 (11.6)

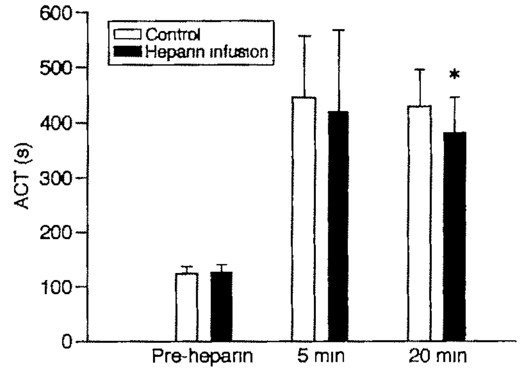

Fig 1 Activated clotting time (ACT, in s) in heparin-naive (controls, group C) patients and patients receiving i.v. heparin for more than 72 h (group H) before coronary artery surgery. Measurements at baseline (pre-heparin), 5 and 20 min after 300 IU kg^{-1} heparin in patients for coronary artery graft surgery For further details see text. Results are mean (SD) for n=18/24 *Significant difference between control and heparin infusion groups (P<0.05)

admitted to group H. The study conformed to local hospital ethics committee guidelines. Exclusion criteria were age over 75 yr, surgery other than first-time coronary artery grafts, patients not requiring CPB and the administration of any anticoagulants other than i.v. heparin.

All blood samples were taken either from the arterial cannula after the removal of 15 ml of blood and fluid from the connecting catheter or directly from the bypass circuit. Anaesthesia was induced with fentanyl (15 µg kg^{-1}) and a sleep dose of either thiopentone or etomidate, and pancuronium (0.1 mg kg^{-1}); anaesthesia was maintained with halothane. Arterial and internal jugular cannulae were inserted and connected to an infusion of saline (0.9% w/v) with sodium heparin 1 U ml^{-1} (Leo Laboratories, Princes Risborough, UK) running at 3 ml h^{-1} to maintain cannula patency. Before cannulation of the aorta, sodium heparin was given i.v. at a dose of 300 IU kg^{-1}. Cannulation was performed and the patient commenced on CPB. Blood was analysed for ACT (Hemochron 401; Technidyne Corporation, Edison, NJ, USA), haematocrit, heparin concentration, AT-3, thrombin–antithrombin complex (TAT-c), prothrombin fragment F_{1+2} (PF_{1+2}) and D-dimers after induction of anaesthesia but before sternotomy, and 5 and 20 min after establishing CPB. If the first dose of heparin did not achieve an ACT of greater than 400 s at 5 min of CPB, a further 5000 IU of heparin was given; if this still did not achieve an ACT of greater than 400 s, this was accepted and no further heparin was administered.

Assays

Prothrombin fragment F_{1+2}, TAT-c and D-dimers were all measured using commercial ELISA kits from Dade Behring (Walton Manor, Milton Keynes, UK); the kits were Enzygnost F_{1+2} micro, Enzygnost TAT micro and Enzygnost D-dimer micro respectively. Antithrombin was measured with a chromogenic kit (Coamatic Antithrombin; Chromogenics, Quadrateck, Epsom, UK). Heparin concentration was measured using a heparin anti-Xa assay (Organon-Teknika, Boxtel, Netherlands) with appropriate dilutions of patients' samples. All the tests were performed according to the manufacturer's instructions.

Statistics

Results are mean (SD). Paired and unpaired Student's t tests were used throughout except for the numbers of patients in each group requiring second doses of heparin, which were analysed with the χ^2 test. Linear regression analysis by the least-squares method was performed for each measurement with ACT as a continuous independent variable. Significance was set at P<0.05.

Results

Complete data were obtained for 24 patients in group H and 18 in group C. The patients in group H received a mean (SD) dose of heparin of 1106 (220) IU h^{-1} for 7.5 (0.8) days. Heparin was stopped 3.5 (0.4) h before surgery. There was no significant difference in age, height, weight, number of grafts performed or time of CPB between the two groups (Table 1). There was no significant difference in the haematocrit between the two groups at any time point (data not shown).

Eight out of 18 patients in group C and 10 out of 24 in group H required a second dose of heparin because the ACT 5 min after the start of CPB was less than 400 s (not statistically significant). The ACT was significantly lower at 20 min in group H than in group C [387 (64) *vs* 432 (55) s, P<0.05] but at all other times there was no significant difference between the two groups (Fig. 1). If patients receiving a second dose of heparin are excluded, the mean ACT at 20 min was 397 (58) (group H) and 448 (69) s (group C) (P=0.067). Despite this, plasma heparin concentrations were similar (Fig. 2A). AT-3 was significantly less in group H 5 min after starting CPB (P<0.05) and approached significance (P=0.052) at 20 min (Fig. 2B). A weak correlation between AT-3 and ACT was observed in control patients 5 min after commencement of CPB (r^2=0.343, p=0.01) but no correlation was observed between any measured variable and ACT at any other time point in either group (data not shown).

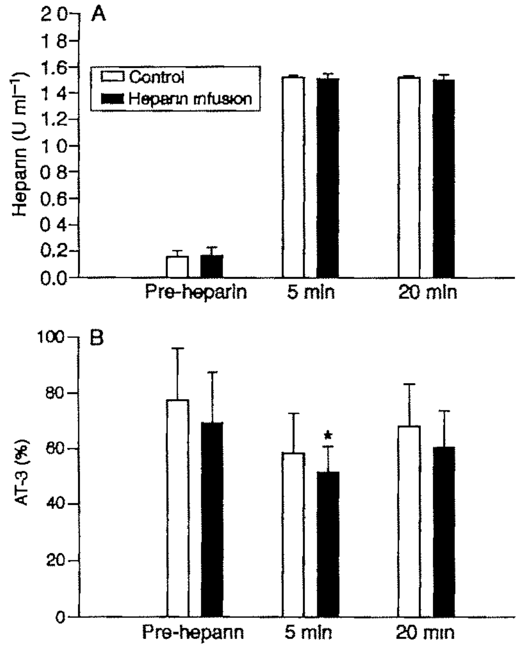

Fig 2 (A) Heparin concentration (anti-Xa, U ml^{-1}) and (B) antithrombin-3 concentration (AT-3,%) in control and heparin infusion patients For further details see text and legend to Fig 1 Results are mean (SD) for n=18/24 *Significant difference between control and heparin infusion groups (P<0.05)

There was no significant difference between the two groups in activation of coagulation as measured by TAT-c, PF_{1+2} and D-dimers at any time point (Fig. 3).

Ten of the 18 controls and 19 of the 24 patients in the heparin infusion group had an ACT less than 400 s 5 or 20 min after commencing CPB (this was not statistically significant). When those with ACT<400 s were compared with those with ACT>400 s in the same group, the only marker of coagulation showing a significant difference was TAT-c at 20 min in group H [18.3 (10.2) μg litre^{-1} in ACT>400 s and 44.9 (22.5) μg litre^{-1} in ACT<400 s]. Unexpectedly, AT-3 in those patients in group H with all ACT>400 s was significantly lower [45.3 (8.3)%] than in those with an ACT<400 s [53.8 (7.8)%, P<0.05]. There was a similar difference between the corresponding values in group C [50.4 (8.5)% in ACT>400 s *vs* 65.8 (11.4)% in ACT<400 s; P<0.05].

Three patients in group C and 10 in group H had an ACT<350 s at either 5 or 20 min. When these two subgroups were compared within their parent group, the pre-CPB AT-3 in those patients of group C who subsequently had ACT<350 s was significantly lower than those with all ACT>350 s [83.4 (15.7)% in ACT>350 s and 48.8 (15.3)% in ACT<350 s; P<0.01]. There was no significant difference between the measurements of activation of coagulation between the subgroups. No patients had an ACT<300 s.

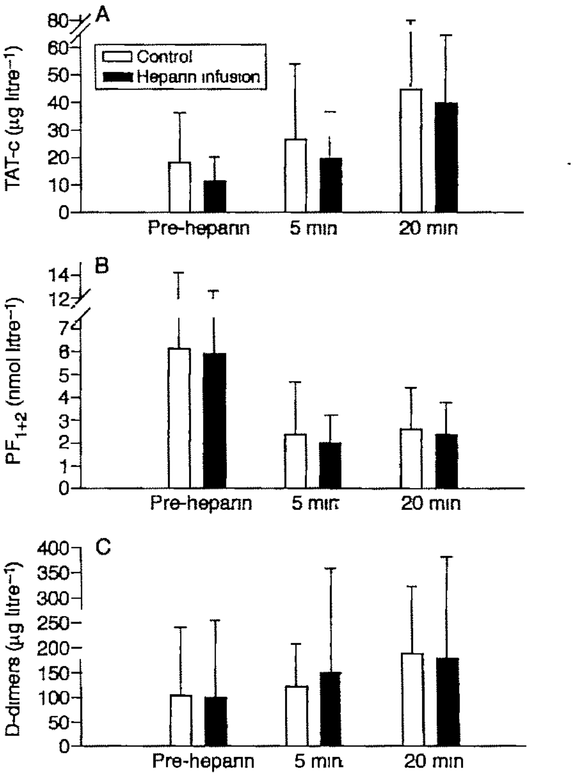

Fig 3 Indices of coagulation (A) Thrombin–antithrombin complex (TAT-c, μg litre^{-1}). (B) Prothrombin fragment F_{1+2} (PF_{1+2}, nmol litre^{-1}). (C) D-dimers (μg litre^{-1}). For further details see text and legend to Fig. 1. Results are mean (SD) for n=18/24 No significant differences between groups.

Discussion

An ACT of more than 400 s is widely considered to indicate adequate heparinization/anticoagulation for patients undergoing CPB, but the basis for this arbitrary level is uncertain and the safe lower limit of ACT is undefined. In particular, the relationship of this measurement to the phenomenon of heparin resistance is obscure. We examined some indices of coagulation and anticoagulation in patients having prior heparin infusion to determine whether possible heparin resistance is clinically important, if ACT is the sole measure of anticoagulation. Therefore, although ACT was analysed as a continuous variable, the effects of ACT values less than 400 and 350 s were examined as clinically relevant divisions.

In contrast to other groups,[2 3 8 12] we did not show a decreased response to initial heparin dose in patients receiving i.v. heparin therapy before cardiac surgery, although at 20 min of CPB the ACT was significantly less in the heparin group, which may indicate an overall increased requirement for heparin.

The AT-3 concentration was lower at all times in the heparin infusion group, but this only reached statistical significance 5 min after CPB. The AT-3 concentration was lower in the few control patients who had an ACT of less than 350 s after heparinization at either 5 or 20 min of CPB, but this difference was not seen between the two heparin groups with ACT greater than or less than 350 s. Therefore, our findings, based on relatively small numbers, cannot statistically support the theory that long-term heparin infusion decreases AT-3[4] or that this is responsible for the heparin resistance, as those patients with ACT<400 s in both the control and heparin groups had AT-3 concentrations greater than those who showed no heparin resistance. There was no correlation between AT-3 and heparin concentrations in either group.

In no case was the degree of activation of coagulation pathways greater in patients given heparin infusions than in patients in the control group. Both TAT-c and D-dimers increased over the operative period in both groups, which is the response seen to all surgery, not just that involving CPB.[13] TAT-c was greater in the subgroup of heparin-infused patients who had ACT <400 s compared with those with ACT >400 s; however, this was not supported when the arbitrary division was taken as 350 s, or in the control group using either subdivision. This cannot be seen to be evidence of activation of coagulation.

The choice of ACT above which anticoagulation for CPB is considered to be adequate to prevent coagulation has always been controversial. Bull and colleagues[1] suggested that below 300 s coagulation was activated and suggested a choice of 480 s as a safeguard, so that the value of 300 s was never reached. By measuring markers of activation of coagulation, Young and colleagues[14] demonstrated that below 348 s activation was seen in rhesus monkeys, and rounded this figure up to 400 s. Gravlee and colleagues[11] measured the activation of coagulation in humans and stated that ACTs greater than 350 s were not associated with any greater activation of coagulation. This is often interpreted to mean that the ACT should never fall below 400–480 s and a lower value is unacceptable. This encourages the practice of giving greater doses of heparin with all the attendant disadvantages of increased postoperative blood loss. We confirmed that, even when the ACT fell to less than 350 s no activation of coagulation was seen. Perfusionists, blinded to the ACT and patient group, reported no clotting in their pumps or problems with the oxygenators and there were no differences in the postoperative outcomes of the two groups at 24 h (data not shown). Perhaps the way to avoid the peaks of anticoagulation in these cases is to accept the lower ACT but to measure it more frequently. This study supports the theory that a heparin dose of 300 IU kg^{-1} provides a safe level of anticoagulation for CPB even in patients on heparin infusions.

ACT measurements are a convenient and hence common but crude measure of heparin anticoagulation. The divergence of results mentioned above suggests that it is not as useful as once considered. Heparin levels have been used to monitor heparinization in patients treated for deep vein thrombosis, but their use in CPB has not been widespread.[15] We have confirmed the findings of other workers[11] that the heparin concentration showed no significant difference between the groups at any time and did not correlate with the ACT. Possibly the time has come to move away from these older tests in favour of more sophisticated monitoring of heparinization and anticoagulation status.

Acknowledgement

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Safety of oral nicorandil before coronary artery bypass graft surgery†

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Nicorandil is a K_{ATP} channel opener used to treat angina. It is cardioprotective and a vasodilator. We conducted a prospective, randomized, double-blind, placebo-controlled study to assess oral nicorandil in patients undergoing coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB). Twenty-two patients received nicorandil (10 mg twice a day) and 23 patients received placebo. Haemodynamic data were recorded before induction of anaesthesia (T0), 5 and 20 min after starting mechanical ventilation (T1, T2), before aortic cannulation (T3), after 30 min of CPB (T4), 10 min after CPB (T5) and after 3, 8 and 18 h in the intensive care unit (T6, T7, T8). Serum proteins (creatine kinase metabolite and cardiac troponin I) were measured before and 8 and 18 h after surgery. Haemodynamic values did not differ between the two groups. There was no tachycardia during the study, no significant difference in hypotensive episodes, ST segment changes and no changes in cardiac enzymes. Myocardial infarction after surgery was similar in the two groups. Vasoactive therapy was similar in the two groups. Nicorandil can be continued safely up to premedication without deleterious haemodynamic consequences, but a myocardial protective effect of nicorandil in CABG surgery was not found.

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Nicorandil is an ATP-dependent potassium (K_{ATP}) channel opener used to treat angina.[1 2] K_{ATP} channels are found in cardiac muscle and vascular smooth muscle. Nicorandil dilates arteries and veins: potassium channel activation leads to calcium channel blockade and arterial dilation, while the nitrate moiety dilates veins by increasing intracellular cyclic guanosine monophosphate (cGMP).[3] Nicorandil dilates peripheral and coronary vessels and increases coronary blood flow, reduces preload by increasing venous capacitance and afterload by decreasing peripheral resistance.[2–4] Nicorandil may be cardioprotective by opening K_{ATP} channels, as suggested by animal studies of ischaemia–reperfusion injury in stunned and infarcted myocardium. Nicorandil reduced infarct size and improved systolic shortening after short-term coronary occlusion.[5]

We conducted a prospective, randomized, double-blind, placebo-controlled study of the safety of oral nicorandil in patients undergoing coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB). We studied

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Table 1 Patient characteristics. *Mean (SD). *n* = number of patients/or grafts; ACE = angiotensin-converting enzyme $P>0.05$ for all criteria (unpaired *t*-test)

	Nicorandil group (n=22)	Placebo group (n=23)
Age (yr)*	64 (9)	63 (10)
Sex (M/F, n)	19/3	22/1
Height (cm)*	169 (9)	167 (7)
Weight (kg)*	80 (14)	74 (14)
Medical history (n)		
Systemic hypertension	11	9
Myocardial infarction	12	14
Heart failure	1	0
Associated valve disease	1	0
Diabetes mellitus	5	5
Preoperative medications (n)		
β-Blockers	17	20
Diltiazem or verapamil	5	5
ACE inhibitors	7	9
Trimetazidin	8	6
Cholesterol-lowering agents	8	5
Anticoagulant agents	3	0
Antiplatelet treatment	19	21
Coronary disease severity		
Left main vessel stenosis >75% (n)	2	1
Double vessel disease	3	6
Triple vessel disease	19	17

the effect of routine nicorandil treatment on cardiovascular changes during and after surgery, the possible cardioprotective effects of nicorandil based on the incidence of ischaemic episodes, and the effect of CPB on the pharmacokinetics of nicorandil.

Methods

Patients about to undergo elective CABG were recruited by a single cardiologist. Inclusion criteria were age between 18 and 75 yr, stable angina and a left ventricular ejection fraction (LVEF) >40%. Patients already taking nicorandil, nitrates, dihydropyridines and sulfonylureas were excluded. The patients were randomized into two groups: nicorandil 10 mg twice daily and placebo groups. Treatment started on the evening of recruitment up to a maximum of 1 month before surgery. All patients had a preanaesthetic consultation at least 7 days after inclusion, with baseline heart rate and arterial pressure measurements. A 12-lead ECG was recorded, biochemical and haematological tests were done, and compliance with medication was recorded.

In patients taking inhibitors of angiotensin-converting enzyme (ACE), treatment was stopped 24 h before surgery. Patients taking β-adrenergic blocking agents received their usual dose on the morning of surgery. The study treatment was given up to the time of premedication, approximately 2 h before induction of anaesthesia.

Patients were operated on by two surgeons. CABG was done with CPB with moderate hypothermia (34°C) and intermittent, cold, anterograde, crystalloid cardioplegia (Fresenius, Bad Homburg, Germany). Cardiovascular measurements included heart rate, systemic artery, central venous, pulmonary artery and capillary wedge pressures, cardiac output and mixed venous oxygen saturation (Sv_{O_2}) with a Swan–Ganz catheter (Baxter, Irvine, CA, USA). Data were recorded at the following times: before induction of anaesthesia (T0); 5 min after starting mechanical ventilation (T1); 20 min after starting mechanical ventilation (T2); immediately before aortic cannulation (T3); after 30 min of CPB (T4); 10 min after the end of CPB (T5); after 3 h in the intensive care unit (ICU) (T6); after 8 h in the ICU (T7); and after 18 h in the ICU (T8). During and after surgery, we noted hypotensive events ($\geqslant$30% compared with baseline value), tachycardia (defined as any increase in heart rate of $\geqslant$20% compared with baseline value), ST segment elevation $\geqslant$2 mm and ST depression $\geqslant$1 mm lasting more than 1 min. Vasoactive treatment, fluid administration and adverse events were noted up to 24 h after surgery. Serum glutamic oxaloacetic acid transferase, creatine kinase, creatine kinase isoenzymes (CK-MB) and cardiac troponin I (cTnI) were measured and ECGs were recorded at T6 and T8. If CK-MB was higher than 40 IU litre^{-1}, further samples were taken at 24 and 48 h. The plasma concentration of nicorandil was measured at premedication (T–1), T0, T2, T3, T4, T5, T6, T7 and T8. Blood samples were collected in lithium heparin tubes, centrifuged at 4°C at 3500 r.p.m. and the samples stored at –20°C. Nicorandil was measured by semiselective extraction and high-performance gas chromatography.

The anaesthetic was standardized. Oral premedication was with preoperative β-blocker, hydroxyzine 100 mg and midazolam 0.2 mg kg^{-1}. Lidocaine-prilocaine cream (Emla; AstraZeneca, Rueil-Malmaison, France) was applied to the neck 90 min before inserting Swan-Ganz catheter into the right jugular vein. Anaesthesia was induced with midazolam 0.2 mg kg^{-1}, fentanyl 15 μg kg^{-1} and pancuronium 0.1 mg kg^{-1}, all i.v. Anaesthesia was maintained with fentanyl (250 μg) and isoflurane if necessary after 20 min (after T2), to keep arterial pressure within 30% and heart rate within 20% of the baseline values. Hypertension was first treated by additional anaesthetic agents. When this was insufficient, either nicardipine (0.5 mg) or urapidil (2.5 mg) were given. A decrease in blood pressure by more than 30% of the baseline value was treated either by an infusion of hydroxyethylstarch 6% (Elohes 6%; Fresenius Kabi, Sèvres, France) or 3–6 mg ephedrine i.v. Postoperative analgesia was with propacetamol (2 g every 6 h) and morphine was given by continuous i.v. infusion (20–40 mg 24 h^{-1}).

Statistics

Results are expressed as mean and standard deviation. Patient characteristics were compared by the *t*-test Cardiovascular values were compared by two-way analysis of variance for repeated measurements followed by the Tukey test when appropriate. $P<0.05$ was considered significant. Statistical analysis was done with SPSS 9.0 for Windows (SPSS BI, Paris, France). To assess sample size,

Table 2 Perioperative cardiovascular measurements. Results are expressed as mean (SD). HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; CVP = central venous pressure, PCWP = pulmonary capillary wedge pressure, CI = cardiac index, Sv_{O_2} = mixed venous oxygen saturation; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; NA = not available

	T0	T1	T2	T3	T4	T5	T6	T7	T8
HR (beats min^{-1})									
Placebo	62 (10)	65 (14)	65 (13)	76 (14)	NA	83 (11)	91 (15)	82 (12)	83 (9)
Nicorandil	62 (11)	64 (10)	63 (11)	77 (17)	NA	85 (9)	88 (12)	85 (14)	84 (13)
MAP (mm Hg)									
Placebo	99 (15)	85 (13)	85 (14)	79 (11)	71 (7)	78 (10)	83 (14)	82 (10)	86 (11)
Nicorandil	101 (11)	81 (12)	83 (17)	78 (11)	74 (10)	80 (8)	90 (10)	89 (13)	90 (10)
MPAP (mm Hg)									
Placebo	19 (6)	19 (6)	19 (6)	15 (4)	NA	20 (5)	21 (4)	19 (4)	19 (3)
Nicorandil	18 (6)	17 (4)	18 (5)	13 (4)	NA	17 (4)	19 (5)	18 (5)	20 (2)
CVP (mm Hg)									
Placebo	8 (5)	9 (3)	9 (4)	5 (3)	3 (2)	7 (3)	10 (2)	9 (2)	9 (3)
Nicorandil	8 (3)	8 (2)	8 (3)	5 (3)	3 (3)	7 (3)	9 (3)	9 (3)	9 (2)
PCWP (mm Hg)									
Placebo	12 (5)	10 (4)	11 (4)	8 (4)	NA	11 (4)	11 (3)	10 (3)	11 (3)
Nicorandil	10 (4)	10 (3)	10 (4)	7 (3)	NA	10 (4)	11 (4)	10 (4)	11 (4)
CI (litre min^{-1} m^{-2})									
Placebo	2.5 (0.4)	2.4 (0.7)	2.4 (0.7)	2.7 (0.8)	2.3 (0.3)	3.2 (0.9)	3.1 (0.7)	2.9 (0.9)	2.8 (0.6)
Nicorandil	2.4 (0.4)	2.3 (0.9)	2.4 (0.9)	2.5 (0.8)	2.2 (0.2)	3.0 (1.0)	3.4 (1.3)	3.1 (0.9)	3.1 (0.7)
Sv_{O_2} (%)									
Placebo	75 (6)	80 (5)	80 (5)	80 (5)	77 (10)	84 (5)	85 (5)	86 (5)	87 (5)
Nicorandil	76 (5)	81 (6)	81 (9)	80 (5)	75 (5)	74 (8)	75 (5)	75 (5)	73 (5)
SVR (dyn s cm^{-5})									
Placebo	1610 (333)	1497 (343)	1488 (344)	1289 (322)	1377 (283)	1045 (260)	1080 (256)	1200 (291)	1264 (302)
Nicorandil	1646 (339)	1414 (349)	1558 (627)	1357 (518)	1417 (346)	1073 (244)	1090 (277)	1174 (472)	1145 (286)
PVR (dyn s cm^{-5})									
Placebo	125 (40)	193 (84)	147 (71)	117 (43)	NA	126 (57)	151 (58)	147 (48)	130 (46)
Nicorandil	137 (84)	140 (75)	142 (64)	101 (40)	NA	111 (59)	120 (44)	130 (110)	133 (68)

we considered changes in arterial pressure. To demonstrate a difference of 10 mmHg in arterial pressure between the groups, given a standard deviation of 10 mmHg with a power of 90%, each group would have to contain 25 subjects.

Results

We enrolled 51 patients. Six patients were excluded for the following reasons: one patient in the placebo group had an LVEF <40% (inclusion mistake); one patient in the nicorandil group died from a cerebral stroke before admission for surgery; and four patients (three in the nicorandil group and one in the placebo group) had poor compliance with the study medication.

Table 1 gives patient characteristics. There was no statistically significant difference between the groups in surgical characteristics, such as the number of CABGs performed, the surgeon, or the duration of CPB or aortic cross-clamping. Anaesthetic dosage was similar in the two groups.

Cardiovascular changes (Table 2) did not differ between the two groups. The lowest mean arterial pressure (MAP) was observed during CPB [74 (10) mm Hg in the nicorandil group and 71 (7) mm Hg in the placebo group]. Systemic vascular resistance was lowest at T5 and T6 during the rewarming period, associated with a simultaneous increase in cardiac index in both groups.

Table 3 shows the number of patients with one or none or with three or more hypotensive events recorded during the three intervals T0–T3, T3–T5 and T5–T8 and the number of therapeutic interventions to restore blood pressure (volume infusion or ephedrine treatment). There was no difference between the nicorandil and placebo groups. There were no episodes of tachycardia (as defined above, under Methods) during the study. There was no statistically significant difference in the number or pattern of distribution of ST segment changes between the groups.

Cardiac enzyme changes are shown in Figure 1. The differences between the groups were not significant. Ten patients had myocardial damage (CK-MB >40 IU litre^{-1} or cTnI >9 μg litre^{-1}; three patients in the nicorandil group and

Table 3 Number of patients with hypotensive events or at least one episode of significant ST change. *Number of interventions given in parentheses. No significant difference between groups

Period	More than one hypotensive event (therapeutic intervention)*	More than three hypotensive events (therapeutic intervention)*	At least one significant ST change
Before surgery			
Nicorandil (n=22)	NA	NA	5
Placebo (n=23)	NA	NA	4
T0–T3			
Nicorandil (n=22)	9 (2)	3 (1)	0
Placebo (n=23)	7 (2)	3 (3)	3
T3–T5			
Nicorandil (n=22)	11 (1)	3 (1)	2
Placebo (n=23)	12 (2)	5 (2)	1
T5–T8			
Nicorandil (n=22)	3 (0)	2 (2)	5
Placebo (n=23)	7 (3)	2 (2)	6

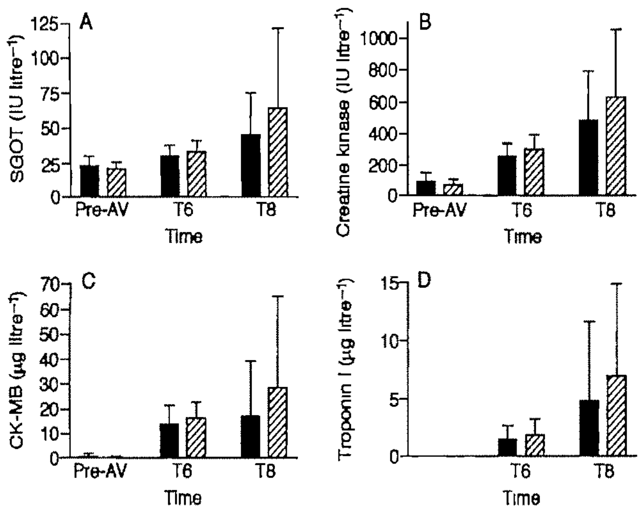

Fig. 1 Changes in cardiac enzymes. (A) Serum glutamic oxaloacetic acid transferase. (B) Creatine kinase. (C) Creatine kinase metabolite. (D) Troponin I. There was no statistical significant difference between groups. Black columns = nicorandil group; grey columns = placebo group; pre-AV = preanaesthesia visit; T6 = after 3 h in ICU, T8 = after 18 h in ICU

seven in the placebo group). There was no significant difference between the groups. Postoperative ECGs did not show new Q waves in patients with increased cardiac enzymes.

Nicorandil concentrations in the nicorandil group (22 patients) are shown in Figure 2. Nicorandil was not found in the plasma of the patients of the placebo group.

Fluid requirements were similar in the two groups, with a median volume infusion of 500 ml of hydroxyethylstarch 6% in 15 patients in the nicorandil group and 16 patients in the placebo group, administered mainly during rewarming. The only patient requiring transfusion (600 ml of red cells) in the nicorandil group needed surgical re-exploration, whereas four patients in the placebo group received transfusion [mean volume 550 (300) ml] without surgical re-exploration. Vasoactive treatment after operation, such as epinephrine infusion (one patient in the nicorandil group and two patients in the placebo group), vasodilators, such as nicardipine [11 patients in the nicorandil group (median dose 5.5 mg) *vs* nine patients in the placebo group (median dose 2.0 mg)] and urapidil (five patients in the nicorandil group *vs* three patients in the placebo group with the same median dose of 20 mg), and also drugs used to decrease heart rate (β-blocker or diltiazem according to preoperative management) were similar in the two groups (three patients in the nicorandil group *vs* two patients in the placebo group).

Discussion

We found that nicorandil medication during cardiac surgery had neither adverse cardiovascular effects nor cardioprotective effects.

Haemodynamic tolerance

Nicorandil treatment, increased progressively up to a dose of 80 mg day^{-1}, did not cause a symptomatic decrease in arterial blood pressure or heart rate and could be combined with other antianginal drugs.[1] Total vascular resistance decreased slightly after an oral dose of 30 mg.[4] The usual dose in patients with ischaemic heart disease is 20 mg day^{-1}, but patients with heart failure may need more to obtain consistent responses because of less bioavailability.[6]

In the present study, there were no cardiovascular differences even in the presence of preoperative treatment with β-blockers and/or calcium channel blockers. In dogs, giving nicorandil during isoflurane anaesthesia reduced systolic arterial pressure and caused reflex tachycardia

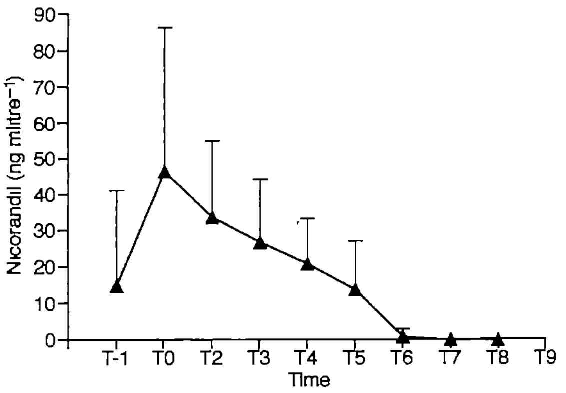

Fig. 2 Plasma concentration of nicorandil in the nicorandil group (n=22)

without myocardial dysfunction.[7] In the present study, the lack of nicorandil-induced haemodynamic effects can be explained by the less marked cardiovascular effects of the anaesthetic.

The number of therapeutic interventions was much lower than the number of hypotensive episodes because the baseline arterial pressure value was determined in the awake patient. A 30% reduction in arterial pressure (defined as a significant hypotensive event in the study) was not always considered to need treatment in an anaesthetized patient, particularly when the baseline systolic arterial pressure could be 150 mm Hg.

The effects of nicorandil during CPB are not well documented. Large requirements for phenylephrine and inotropic agents to maintain perfusion pressure above 55 mmHg during CPB have been reported in seven patients taking oral nicorandil preoperatively, which persisted for 4–72 h after CPB in some patients.[8] The haemodynamic effects of nicorandil could be exaggerated by depletion of adenosine triphosphate, which can occur during CPB. Our study suggests that severe collapse is unlikely when chronic treatment with nicorandil is maintained until premedication.

Myocardial protection

The cardioprotective effects of nicorandil have been studied experimentally.[5] [9] Nicorandil gives the same degree of myocardial protection as ischaemic preconditioning, limits infarct size after irreversible ischaemic injury and attenuates myocardial 'stunning' after briefer, reversible periods of ischaemia.[3] This protection is prevented by the administration of a potassium channel blocker, such as glibenclamide or sodium 5-hydroxydecanoate, indicating the involvement of the K_{ATP} channels.[10 11] Consequently, the use of potassium channel openers such as nicorandil could enhance cardioplegic protection in cardiac surgery.[12] Nicorandil also enhances cardioplegic protection by reducing ischaemic contracture during reperfusion, reducing the effects of ischaemic arrest and improving postischaemic recovery of contractile function.[12 13]

No protective myocardial effect was found in the present study. Despite a trend to smaller concentrations of markers of cardiac damage and less postoperative myocardial infarction in the nicorandil group, statistical significance was not found, perhaps because the sample size was too small.

A protective myocardial effect of nicorandil may not have been found for several reasons, which will be discussed below.

Plasma concentrations of nicorandil

Patients had a nicorandil concentration in the therapeutic range, with minimum values reaching almost 10 ng ml^{-1} and persisting until T4. The greatest concentration was at T0 [46.5 (40.1) ng ml^{-1}], 2 h after the last dose taken with the premedication. In healthy subjects, after a single dose of oral nicorandil, the mean maximum plasma concentration was 107 (30) ng ml^{-1} (range 44–148), usually between 30 and 60 min after administration. The discrepancy between the apparent short elimination half-life of nicorandil (1 h) and a persistent effect on exercise angina (observed 6 h after administration) is attributed to the affinity of nicorandil for vascular tissues. This tissue distribution pattern of nicorandil may support its duration of action.[14]

Cardioprotective effects from nicorandil during CPB may require the higher plasma concentrations given by i.v. administration before onset of CPB or by addition to cardioplegic solutions.[12] [13] Clinical studies remain to be performed.

At the end of CPB (T5), mean nicorandil concentration decreased to the value found at T–1, which is the concentration 12 h after oral administration. This may have been caused by CPB dilution. Three hours after arrival in the ICU (T6), nicorandil had almost completely disappeared from the plasma.

Vasoactive treatment

β-Adrenergic blocking agents. We gave β-blockers routinely to all patients up to premedication. This may explain the lack of tachycardia noted experimentally[7] [15] or clinically.[16] Perioperative myocardial infarction seems unrelated to preoperative patient characteristics, but is more frequent in patients with perioperative ECG evidence of myocardial ischaemia, particularly in association with tachycardia.[17] A slow heart rate is a major goal in patients with coronary artery disease.[18] Postoperative myocardial infarction was more frequent in patients receiving no antianginal therapy or treated with calcium channel-blocking drugs, than in those treated with β-blockers alone or in combination.[17] [19] β-Adrenergic blocking agents seem effective in patients undergoing either CABG surgery[20] or non-cardiac surgery,[21] by reducing the incidence of perioperative myocardial ischaemia and risk of death at 2 yr.

Therefore, β-blockers are commonly maintained until premedication and resumed as soon as possible after extubation. In this study, the continuation of the β-blockers may have obscured the possible protective effects of nicorandil.

Isoflurane. Isoflurane is a commonly used halogenated anaesthetic agent with dose-related negative inotropic and vasodilatory actions, which are attributed to alterations in voltage-dependent slow calcium channel activity in the sarcolemmal membrane. The antagonization of K_{ATP} channels by glibenclamide suggests that the effect of isoflurane is mediated predominantly by the adenosine receptor activation of the K_{ATP} channels.[22] Experimentally, isoflurane mimics the cardioprotective effects of ischaemic preconditioning by the activation of protein kinase C (PKC) and the opening of K_{ATP} channels, probably at the mitochondrial level.[23] Isoflurane preconditioning of the human heart during cardiac surgery has been reported through a significant increased value of ecto-5′-nucleotidase activity, considered to be a marker of PKC activation, and lower cTnI in patients given isoflurane before CPB.[24] Nicorandil and isoflurane given together can enhance postischaemic recovery of left ventricular function.[25]

Isoflurane was used in both groups as an additional agent to reduce blood pressure changes during the surgical events, such as sternotomy. Both groups could have gained from the use of isoflurane before CPB, which may limit the capacity of the study to demonstrate any cardioprotective effects of nicorandil.

ACE inhibitors. In this study, seven of the 22 patients in the nicorandil group and nine of the 23 patients in the placebo group were treated preoperatively with ACE inhibitors. This treatment is unlikely to have influenced the results of the study because the number of treated patients, although small, was similar, and the values of the haemodynamic variables did not differ significantly between the groups. The known haemodynamic effect of ACE inhibitors on anaesthetic induction led us to maintain our routine practice of stopping treatment 24 h before the scheduled time of surgery.[26]

General tolerance

Nicorandil can cause large and painful mouth ulcers with severe dysphagia.[27] Other side-effects include headache resulting from vasodilation, usually experienced during the first days of treatment and reduced by increasing the dose slowly. Dizziness and gastrointestinal disorders have also been reported.[1 2 28] Except for the patient who complained of headache 6 days after starting treatment (which could have been related to a massive cerebral ischaemic attack), no other side-effect was noticed.

Conclusion

Preoperative treatment with nicorandil, often combined with other antianginal agents, is common in patients with coronary artery disease. We found no adverse perioperative haemodynamic effects, such as hypotension or tachycardia, even when treatment was maintained until premedication. Myocardial protective effects of nicorandil in CABG surgery were not demonstrated.

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Postoperative changes in visual evoked potentials and cognitive function tests following sevoflurane anaesthesia

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We tested the hypothesis that minor disturbance of the visual pathway persists following general anaesthesia even when clinical discharge criteria are met. To test this, we measured visual evoked potentials (VEPs) in 13 ASA I or II patients who did not receive any pre-anaesthetic medication and underwent sevoflurane anaesthesia. VEPs were recorded on four occasions, before anaesthesia and at 30, 60, and 90 min after emergence from anaesthesia. Patients completed visual analogue scales (VAS) for sedation and anxiety, a Trieger Dot Test (TDT) and a Digit Symbol Substitution Test (DSST) immediately before each VEP recording. These results were compared using Student's *t*-test. $P<0.05$ was considered significant. VEP latency was prolonged ($P<0.001$) and amplitude diminished ($P<0.05$) at 30, 60, and 90 min after emergence from anaesthesia, when VAS scores for sedation and anxiety, TDT, and DSST had returned to pre-anaesthetic levels.

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In 1997, 60% of all elective surgical procedures in the USA were done on a 'day case' or ambulatory basis.[1] In these patients, rapid, complete recovery from the effects of anaesthetic agents is desirable. Clinical, psychomotor, and cognitive tests can measure recovery from the residual effects of anaesthetic agents.[2 3] Although cognitive and psychomotor tests are normal by the second day after operation, subjective cognitive impairment can persist for 3 days.[4] Patients who have been discharged probably have minor degrees of residual anaesthetic effect, with implications on safety as patients resume normal activities of daily living.

The effect of anaesthetic agents on visual evoked potentials (VEPs) has not been studied in the postoperative period. Minor degrees of disturbance of the visual pathway could persist following general anaesthesia.

Of the evoked potentials in clinical use, VEP is the most sensitive and brainstem auditory evoked potentials are the most resistant to drug effects.[5 6] Because hearing is the last sensory modality to be abolished and the first to return at light levels of anaesthesia, the effects of anaesthesia on the auditory evoked potentials are well known, in relation to monitoring depth of anaesthesia.[7] VEPs have been studied mostly in the context of testing the integrity of the visual pathway during surgery near the optic chiasm.[7] Anaesthetic agents (both volatile and i.v.) affect the latency and amplitude of VEP.[5 6 8–10 16–19]

We conducted a prospective observational study (1) to quantify the effect of sevoflurane anaesthesia on VEP amplitude and latency in the early (90 min) postoperative period and (2) to examine the association between VEP changes and standard tests of cognitive and psychomotor function.

Methods

With institutional ethical approval, and having obtained written informed consent, we studied 13 ASA I or II patients about to have non-neurological, elective surgery. Patients with decreased visual acuity or hypo- or hyperthermia were excluded from the study.

No pre-anaesthetic medication was administered. VEPs were recorded on four occasions; on arrival to the anaesthetic room preoperatively and at 30, 60, and 90 min after the operation using a portable four-channel evoked potential monitoring system (Neuropack 4 mini MEB5304K, Nihon

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Kohden, Japan). Three transcutaneous 'active' electrodes were placed on the occiput and an 'indifferent' or reference electrode on the midfrontal region. The electrode impedance accepted at the time of measurement was <5 kOhm. Standard EEG disc electrodes were stuck on the scalp by means of a water soluble conducting EEG paste (Ten 20™, D.O. Weaver and Co., USA) and secured in place using a 'swim cap'. A domestic television set placed at a distance of 1 m was used to generate a pattern reversal stimulus of constant luminance, consisting of black and white checks, which alternate abruptly. Moderate room illumination was used during testing. Pattern stimuli were presented at 2 Hz and 100 measurements amplified and digitally averaged to produce the VEP with automatic estimation of latency and amplitude via an Apple Macintosh computer software (Framefile reporting V2.4). However a neurophysiology technician unaware of the time of the recording (relative to anaesthesia) selected the point of maximal response.

Table 1 Aldrete score

Assessment area	**Score**
Activity (able to move voluntarily or on command)	
Four extremities	2
Two extremities	1
Zero extremities	0
Respiration	
Able to deep breathe and cough freely	2
Dyspnoea, shallow or limited breathing	1
Apnoeic	0
Circulation	
SBP±20 mm Hg of pre-anaesthesia level (morning of surgery)	2
SBP±20–50 mm Hg of pre-anaesthesia level	1
SBP±greater than 50 mm Hg of pre-anaesthesia level	0
Level of consciousness	
Alert	2
Drowsy but arousable on calling	1
No response	0
Colour	
Normal	2
Pale dusky, blotchy, jaundiced, other	1
Cyanotic	0

A Trieger Dot Test (TDT) and a Digit Symbol Substitution Test (DSST) were carried out before the operation and immediately before the VEP recordings at 30, 60, and 90 min after the operation.[11 12] The TDT is a measure of psychomotor function. The subject is presented with a figure composed of 41 dots and asked to connect them by a pencil mark in 40 s or less. A score is assigned according to the number of dots omitted. The DSST is a measure of cognitive function and it has been shown to be sensitive even to small degrees of sedation.[12] To do the test, the subject is asked to integrate visual scanning speed with number substitution for 110 given symbols. The test is scored according to the number of correct entries obtained in 90 s. This test is a sensitive measure for residual cortical dysfunction.[13]

Subjective assessments were made with standardized visual analogue scales (VAS) for sedation and anxiety[14 15] at each timepoint. The VAS consisted of two 100-mm lines, such that 0=minimal impairment and 100=maximal impairment, representing drowsiness (0=fully awake and alert, 100=extremely drowsy) and anxiety (0=calm and 100=excited).

With standard monitoring in place (pulse oximetry, electrocardiography, non-invasive arterial pressure, and inspired and end tidal partial pressures of sevoflurane, nitrous oxide and oxygen (Datex AS/3 monitor, Datex Corp., Helsinki, Finland) anaesthesia was induced with 8% sevoflurane in 100% oxygen. General anaesthesia was maintained by inhalation of clinically indicated concentration of sevoflurane in a 33% oxygen/66% nitrous oxide mixture. Temperature was monitored by a naso- or oropharyngeal thermistor (YSI 400 Series, Mallinckrodt Medical, Inc., St Louis, USA). Intraoperative analgesia was fentanyl (1–1.5 μg kg^{-1}), diclofenac 100 mg p.r., or tenoxicam 20 mg i.v. and a local/regional block with 0.5% bupivacaine. Intermittent positive pressure ventilation was used to maintain $P\text{E}'_{\text{CO}_2}$ between 4.0 and 4.5 kPa. Muscle relaxation, when indicated, was with 0.1 mg kg^{-1} vecuronium and incremental doses as necessary, monitored using a transcutaneous nerve stimulator (MiniStim MS-

Table 2 Patient characteristics, anaesthetic duration, end-tidal (ET) sevoflurane concentration and Aldrete score on arrival in recovery area

Patient no.	**Sex**	**Age (yr)**	**Weight (kg)**	**Anaesthetic duration (min)**	**ET sevoflurane (%)**	**Aldrete score**
2	f	61	60	66	0.20	9
3	m	19	70	59	0.16	9
4	f	44	80	35	0.20	9
5	f	56	70	40	0.20	9
6	m	19	81	112	0.30	9
7	f	49	75	57	0.27	9
8	f	56	58	73	0.19	9
9	f	62	60	45	0.29	9
10	f	38	62	42	0.27	10
11	f	37	70	45	0.24	9
12	m	36	68	64	0.31	10
13	f	21	50	44	0.21	9
Mean		41	67	57	0.23	9.2
SD		15	9	21	0.05	0.4

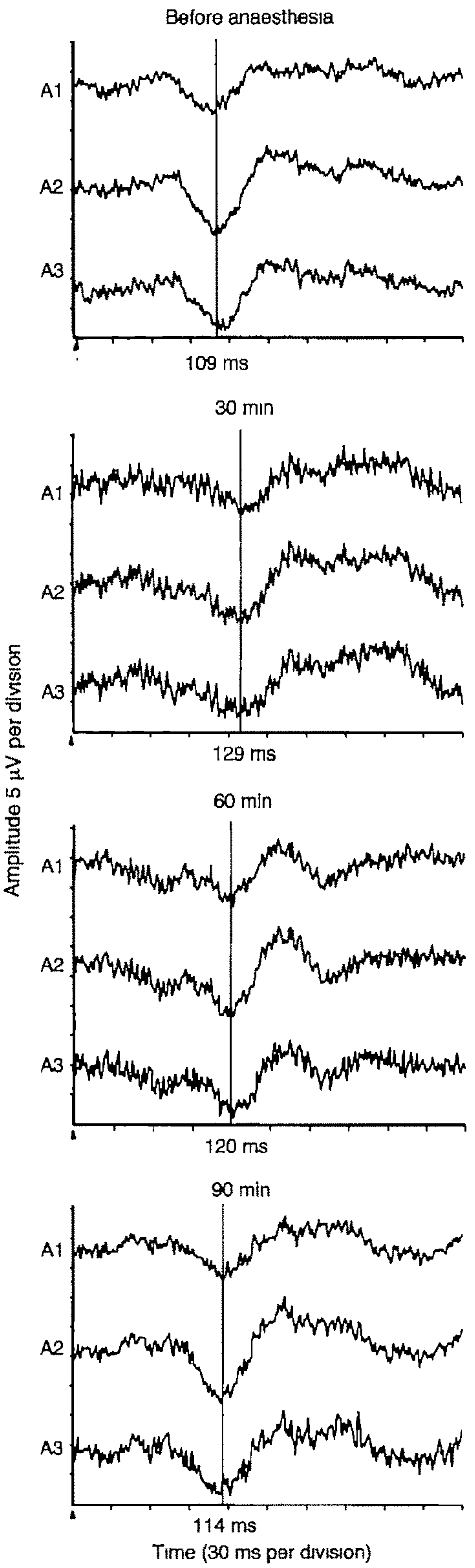

Fig 1 Characteristic VEP recordings from stimulation of the left eye of a patient obtained before (top) and at 30, 60, and 90 min after anaesthesia (bottom) A1-3 represents the recordings from the active electrodes. The cursor indicates the time of maximal evoked response (latency).

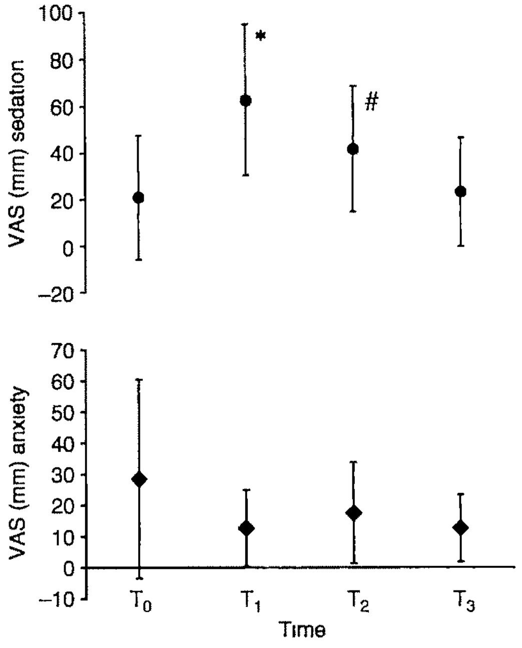

Fig 2 Sedation and anxiety measurements T_0 represents the time before anaesthesia (baseline) T_1, T_2, and T_3 represent 30, 60, and 90 min after emergence from anaesthesia, respectively *P<0.001 compared with pre-anaesthetic values, #P=0.01 compared with pre-anaesthetic scores

IIIA, Life-Tech, Inc., Houston, USA) and antagonized with neostigmine 50 µg kg^{-1} combined with 10 µg kg^{-1} glycopyrrolate. End-tidal sevoflurane ($F\text{E}'_{\text{sevo}}$) concentrations were recorded immediately before tracheal extubation or removal of laryngeal mask airway (LMA)†. On arrival in the postoperative recovery area a post-anaesthesia recovery score of Aldrete and Kroulik[16] was noted (Table 1).

Cognitive (DSST) and psychomotor (TDT) tests, VAS, and VEP measurements were expressed in terms of mean (SD) and compared using Student's *t*-test. *P*<0.05 was considered significant. Correlation was sought between change in VEP amplitude and latency and anaesthetic time, using Pearson's correlation coefficient.

Results

Thirteen (three male and 10 female) ASA I and II patients aged 41 (15, range 19–62) yr were studied. Data obtained from the first patient were not included in the analysis because of inadequate quality of VEP recording caused by large electrode impedance. Seven patients underwent excision of breast lump, three had hysteroscopy, and another three underwent removal of screw/plate from a limb Anaesthesia and analgesia were not standardized. All patients were given fentanyl 1.5 µg kg^{-1}, followed by local infiltration or limb block (one brachial plexus and two combined femoral and sciatic nerve blocks) with 0.5%

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†LMA® is the property of Intavent Limited.

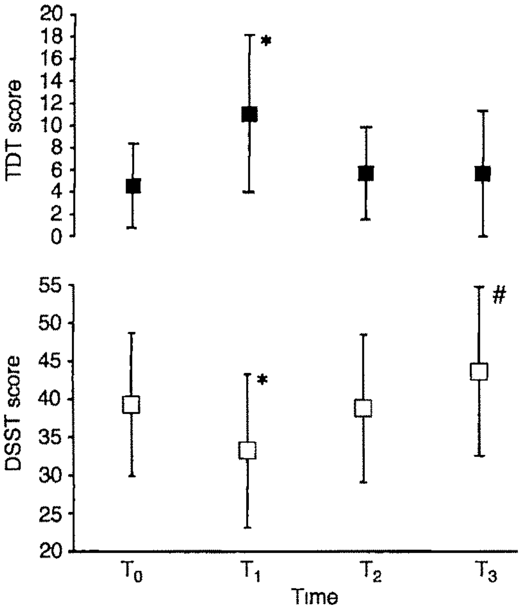

Fig 3 Psychomotor test results. T_0 represents the time before anaesthesia (baseline) T_1, T_2, and T_3 represent 30, 60, and 90 min after emergence from anaesthesia, respectively. *$P \leq 0.001$ and #$P<0.05$ refer to comparison with pre-anaesthetic scores

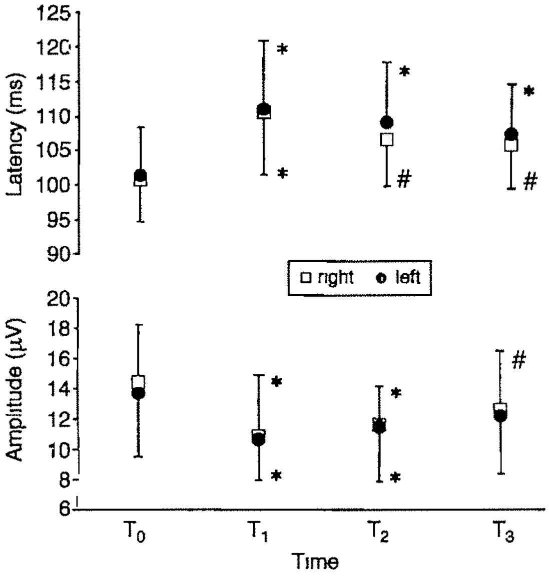

Fig 4 VEP measurements. T_0 indicates the time before anaesthesia (baseline). T_1, T_2, and T_3 represent 30, 60, and 90 min after emergence from anaesthesia, respectively. *$P<0.01$ and #$P<0.05$ compared with pre-anaesthetic values

bupivacaine. Eight patients had diclofenac 100 mg p.r. and five had tenoxicam 20 mg i.v. One patient required a neuromuscular blocking agent (vecuronium 0.1 mg kg^{-1}). Body temperatures were normal.

Duration of anaesthesia was 57 (SD 21) min and end-tidal sevoflurane concentration before tracheal extubation or removal of LMA was 0.23 (0.05). Aldrete scores on arrival in recovery were 10 in two cases and 9 in the remaining 10 cases (Table 2). Characteristic VEP recordings after stimulation of the left eye of a patient at the four times are shown in Figure 1. The latency increased from 109 ms to 129, 120 and 114 ms at 30, 60, and 90 min after the operation, respectively. The amplitude decreased from 15 to 12 µV at 30 and 60 min and returned to 15 µV at 90 min.

Figure 2 shows the VAS for sedation and anxiety. Patients felt more drowsy at 30 ($P<0.001$) and 60 min ($P=0.010$) after emergence from anaesthesia than before anaesthesia. The VAS scores for sedation at 90 min after anaesthesia and the preoperative baseline were not significantly different ($P=0.315$). Pre- and post-anaesthetic anxiety scores were similar.

TDT scores were greater at 30 min ($P=0.001$) after emergence from anaesthesia, but there was no difference at 60 ($P=0.181$) and 90 min ($P=0.251$) compared with the pre-anaesthetic scores (Fig. 3). DSST scores decreased at 30 min ($P<0.001$), were similar to the pre-anaesthetic scores at 60 min ($P=0.39$) and increased at 90 min ($P=0.020$), presumably because of learning (Fig. 3).

The latency of VEP was prolonged at 30 ($P<0.001$ on both sides), 60, and 90 min ($P<0.05$ on the right and $P<0.001$ on the left) after emergence from anaesthesia compared with the pre-anaesthetic values, as shown in Figure 4. The amplitude of VEP was reduced on both sides at 30 ($P<0.01$) and 60 min ($P<0.01$) after emergence from anaesthesia, and this was maintained at 90 min on the right side ($P=0.016$). There was no correlation between the duration of anaesthesia time and changes in VEP latency or amplitude.

Discussion

We found that VEP latency is prolonged 90 min after sevoflurane anaesthesia, when measures of psychomotor and cognitive function and sedation have returned to normal. Thus VEP latency may indicate postoperative residual anaesthetic effect.

Previous studies have shown a dose-related effect of inhalational agents (halothane, enflurane, and isoflurane) on VEP latency and amplitude.[17] Nitrous oxide causes a dose-related decrease in VEP amplitude but not latency.[6 18] Similarly, these findings apply to VEP recorded during anaesthesia, whereas our first VEP measurement was performed 30 min after discontinuation of nitrous oxide administration. Neither fentanyl[19] nor neuromuscular blocking agents[20] influence VEP latency or amplitude. Loughnan and colleagues showed that i.v. fentanyl 200 µg has no effect on evoked potentials.[19] The maximum dose of fentanyl used in our study was 120 µg, so it is likely that the changes in VEP latency and amplitude in this study are related to sevoflurane administration.

Using 'within patient' comparisons, and anaesthesia with a single agent, sevoflurane, known to influence VEP, reduced possible confounding variables. Temperature and systemic arterial pressure can influence VEP,[5] but these were normal in all patients throughout the study. To reduce variation in technique, all VEP recordings were carried out by a single investigator. Latency and amplitude measurement points were then selected by a second investigator who did not know when the recordings had been obtained.

One limitation of this study is that the 'learning effect' for the TDT or DSST was not quantified. The improvement in DSST scores at 90 min suggests that some learning effect was present. The psychometric tests show that no gross deficit in cognitive or psychomotor function is present at the time of prolonged VEP latency.

Although a relatively small number of patients (13) was studied, VEP changes were consistent and varied little between patients.

The changes in VEP latency and amplitude were not related to the duration of anaesthesia. However, duration of anaesthesia is a poor indicator of cerebral anaesthetic partial pressure, especially following discontinuation of volatile agent administration. This may indicate the rapid elimination of sevoflurane particularly following shorter (2 *vs* 4 and 8 h) anaesthesia.[21]

Some degree of 'drowsiness' may have been present as EEG was not recorded at the time that VEP recordings were made. During sleep, the amplitude of the VEP tends to increase.[22] Since in our study the amplitude of VEP, if anything, decreased, our results are unlikely to be attributable to a 'sleep-like' state.

How important is the increased VEP latency or decreased VEP amplitude following anaesthesia? An abnormal VEP does not necessarily indicate that a visual deficit is present.

In conclusion, we found that VEP measurement, a non-invasive, reproducible bedside technique, indicates a residual effect of sevoflurane. In view of previous studies on intraoperative VEP, this effect is likely to be true for other inhalation anaesthetic agents, especially when considering the low blood:gas partition coefficient (0.63–0.69) of sevoflurane. The low solubility of sevoflurane in blood suggests that alveolar:inspired concentrations should decrease rapidly upon cessation of the agent (washout). It is very likely that the effects on VEP latency and/or amplitude persist after current discharge criteria from recovery room are met.

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Influence of oral tramadol on the dynamic ventilatory response to carbon dioxide in healthy volunteers

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We tested the effect of tramadol on ventilatory control by quantifying its effect on the steady-state ventilatory carbon dioxide response and by locating its site of respiratory action within the ventilatory control system. We imposed square-wave changes in end-tidal carbon dioxide (~1 kPa; end-tidal oxygen concentration kept constant at resting levels) in 10 healthy volunteers (six men, four women) before and after oral ingestion of 100 mg tramadol, and measured the ventilatory responses. Each hypercapnic response was separated into a fast, peripheral and a slow, central component. Two control and two tramadol carbon dioxide studies were performed in each subject. Tramadol reduced the total ventilatory carbon dioxide sensitivity by ~30% from 12.8 (6.1) [lower (25%) and upper (75%) quartiles 7.4 and 16.6 litre min^{-1} kPa^{-1}] to 9.1 (5.3) (5.3–14.1) litre min^{-1} kPa^{-1} ($P<0.001$). The fast and slow response gains were reduced by 23 (46) (3–54)% ($P<0.05$) and 30 (22) (15–54)% ($P<0.01$) respectively. The ratio of these carbon dioxide sensitivities and the apnoeic threshold were not significantly changed by tramadol. We suggest that tramadol affects the ventilatory control system by acting at the μ-opioid receptors in the respiratory integrating centres within the brainstem.

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Tramadol is an analgesic with putative opioid and non-opioid modes of action.[1] The respiratory effects of tramadol are not clear: some clinical studies indicate little or no respiratory depression[2–4] but others find significant respiratory effects.[5 6] Several case reports suggest that the respiratory depressant effect of tramadol is usually underestimated.[7 8] These differences could be caused by the different methods used to test ventilatory control, the state of arousal of the subjects or the doses and routes of administration.

We set out to quantify the effect of oral tramadol on ventilatory control in healthy volunteers and to locate its site of action within the ventilatory control system. In order to do so, we used the dynamic end-tidal forcing technique.[9 10] This technique measures the steady-state ventilatory carbon dioxide sensitivity and also estimates the relative contributions of the peripheral and central chemoreflex gains.

We applied square-wave changes in end-tidal carbon dioxide concentration and divided the ventilatory response (measured on a breath-to-breath basis) into a fast, peripheral dynamic component and a slow, central component, using an empirical two-compartment model of the ventilatory controller. This mathematical model has been validated in cats.[11] It has been used in humans to assess the effect of opioids,[12] anaesthetics[13] and catecholamines[14] on ventilatory control.

Methods

Twelve volunteers (aged 22–56 yr; seven men) participated in the study after approval had been obtained from the local human ethics committee. The subjects were healthy and did not smoke tobacco. Subjects were asked not to take caffeine-containing drinks for 8 h beforehand, and fasted for at least 4 h before the studies. They were studied in a semirecumbent position in a well-lit room and listened to music via headphones.

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On the study day, after arrival at the laboratory, electrodes for ECG (Hewlett-Packard 78351A) and EEG electrodes (BisSensor; Aspect Medical Systems, Newton, MA, USA) were placed on the thorax and head respectively. Next, the subjects rested for 10–20 min. The subjects breathed through a facemask (Vital Signs, Totowa, NJ, USA). Expiratory gas flows were measured with a pneumotachograph (Fleisch no. 2) and a pressure transducer (Furness Micomanometer), and the signal was integrated electronically to obtain volume. The inspired gas mixture was set using mass-flow controllers (Bronkhorst High-Tec, Veenendaal, The Netherlands) controlled by a personal computer (Elonex PT-5120/1). This allows the forcing of end-tidal $P\text{O}_2$ ($P\text{E}'_{\text{O}_2}$) and end-tidal $P\text{CO}_2$ ($P\text{E}'_{\text{CO}_2}$) according to a specified pattern in time. The inspired and expired oxygen and carbon dioxide concentrations were measured near the mouth with a mass spectrometer (VG Spectralab M, Winsford, UK) and the arterial haemoglobin oxygen saturation (Sp_{O_2}) with a pulse oximeter (Ohmeda Biox 3700, Ohmeda, Helsinki, Finland) set to give a rapid response. End-tidal oxygen and carbon dioxide partial pressures, tidal volume, inspiratory time (Ti), expiratory time (Te), breathing frequency (f=60/[Ti+Te]), expired minute ventilation ($\dot{V}\text{E}=f \times V\text{T}$) and Sp_{O_2} were collected and stored on disk for further analysis.

The EEG was recorded using an A-2000 EEG monitor (Aspect Medical Systems; software version 3.3). The monitor computed the bispectral index (BIS) over 5-s epochs. We averaged the BIS values over 1-min intervals.

Oxygen consumption (litre min^{-1} standard temperature and pressure, dry (STPD) and carbon dioxide output (litre min^{-1} STPD) were measured from collections of mixed expired gas made over a 2-min period, and the gas exchange ratio was calculated. Concentrations of oxygen and carbon dioxide were measured using a Servomex oxygen analyser (model 570A, Servomex, Norwood, MA, USA) calibrated with air and 100% nitrogen, and carbon dioxide with a Datex analyser (Normocap 200, Datex, Helsinki, Finland) calibrated with four calibration gas mixtures.

The experiments consisted of normoxic steps into and out of hypercapnia. After a period of steady-state breathing (assessed by stable ventilation) with $P\text{E}'_{\text{CO}_2}$ raised 0.1–0.2 kPa above resting values, $P\text{E}'_{\text{CO}_2}$ was increased by ~1 kPa in a stepwise fashion and kept constant for 7 min. Subsequently, $P\text{E}'_{\text{CO}_2}$ was returned to its original value and kept constant for another 7 min. During the experiment, $P\text{E}'_{\text{O}_2}$ was kept constant at resting values. In each subject, two control studies and two tramadol studies were performed. Control runs preceded the drug runs. The drug runs were started 30 min after the subject had taken 100 mg tramadol as two 50 mg tablets (Zydol; Searle). Females were studied within the first 10 days of a normal menses to ensure

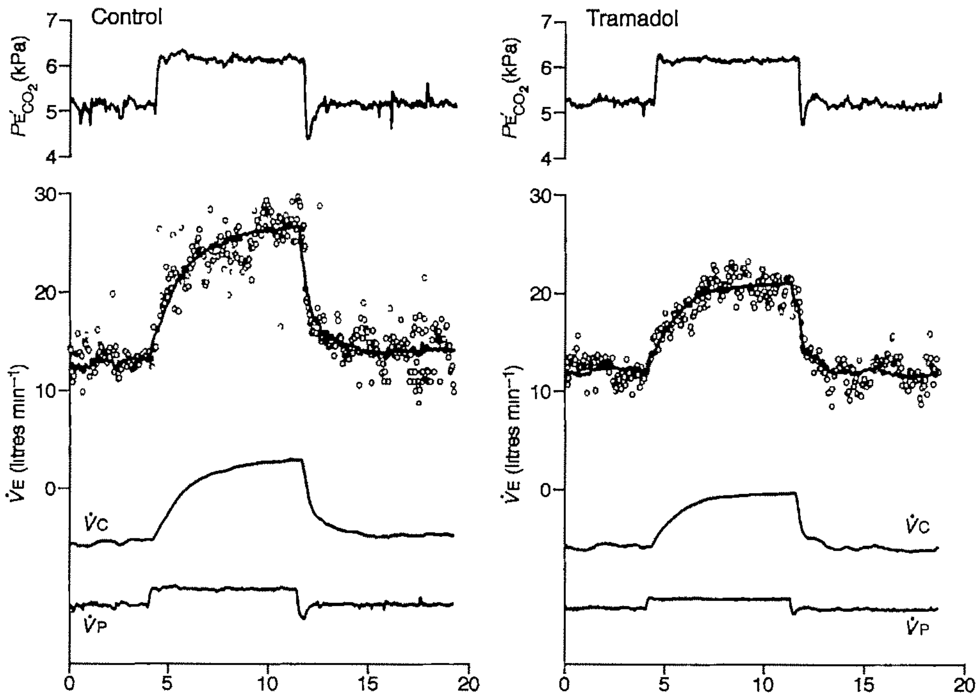

Fig 1 Control (left) and tramadol (right) ventilatory responses to carbon dioxide of one subject. The $P\text{E}'_{\text{CO}_2}$ input function is shown in the top panel. In the middle panel, each circle represents one breath. The thick line through the breaths is the model output, which is the sum of the outputs of the peripheral ($\dot{V}\text{P}$) and central ($\dot{V}\text{C}$) chemoreflex loops and a trend term (not shown). Estimated control values are B=4.1 kPa, G_P=2.1 litre min^{-1} kPa^{-1} and G_C=11.1 litre min^{-1} kPa^{-1} Estimated tramadol parameter values are B=4.0 kPa, G_P=1.6 litre min^{-1} kPa^{-1} and G_C=8.0 litre min^{-1} kPa^{-1}

that they were not pregnant and to avoid any effect of progesterone on ventilation.

The data were analysed by fitting the breath-by-breath ventilatory responses to a two-compartment model, as described previously.[9 10] In short, the steady-state relationship of $\dot{V}_E$ to $P_{E'CO_2}$ at constant $P_{E'O_2}$ is described by the expression

$$\dot{V}_E = (G_P + G_C)\,[P_{E'CO_2} - B]$$

where $\dot{V}_E$ is minute ventilation, G_P is the carbon dioxide sensitivity of the peripheral chemoreflex loop, G_C is the carbon dioxide sensitivity of the central chemoreflex loop and B is the apnoeic threshold or extrapolated $P_{E'CO_2}$ of the steady-state ventilatory response to carbon dioxide at zero $\dot{V}_E$. The sum of G_P and G_C is the total carbon dioxide sensitivity (G_{TOT}). To describe the delay in effect and dynamics of the peripheral and central ventilatory responses to carbon dioxide, time delays and time constants are incorporated in the model. The deterministic model parameters are B, G_C, G_P, the time constant of the peripheral chemoreflex loop, the time constant of the central chemoreflex loop and a linear trend term.[10] The noise corrupting the data was modelled through an external pathway with first-order dynamics.[10] The parameters were estimated with a one-step prediction error method.[15]

The estimated parameters of control and tramadol experiments were tested by two-way analysis of variance. P-values <0.05 were considered significant. All values are given as mean (SD) and the lower (25%) and upper (75%) quartiles.

Table 1 Estimated model parameters. Mean (SD). *Two-way analysis of variance

	Control	Tramadol	P*
B (kPa)	4.6 (0.8)	4.2 (0.8)	0.053
G_C (litre min^{-1} kPa^{-1})	10.8 (5.0)	7.8 (4.9)	0.002
G_P (litre min^{-1} kPa^{-1})	2.0 (1.1)	1.3 (0.5)	0.038
G_{TOT} (litre min^{-1} kPa^{-1})	12.8 (5.7)	9.1 (5.0)	<0.001
G_P/G_C	0.19 (0.09)	0.16 (0.16)	0.88

Results

Control of the $P_{E'CO_2}$ was within 0.18 kPa (i.e. the SD of the breath-by-breath $P_{E'CO_2}$ of single periods was 0.18 kPa or less). $P_{E'O_2}$ was controlled within 0.26 kPa. Data from two subjects were discarded because of consistently irregular breathing, which made estimates of the model parameters impossible.

Mean age of the remaining subjects was 33 (7) (29–37) yr, weight 72 (14) (65–78.75) kg and height 170 (11) (160.0–180.75) cm. All subjects finished the measurements without side-effects.

Examples of a control and a tramadol hypercapnic experiment and model fits of one subject are given in Fig.

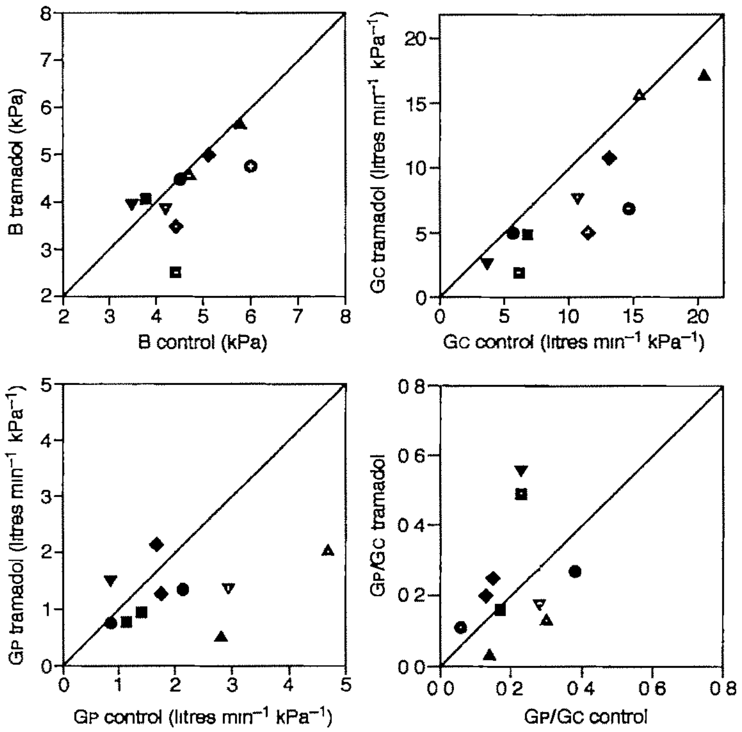

Fig 2 Scatter diagrams of the mean values in each subject of the apnoeic threshold (B) (top left), central carbon dioxide sensitivity (G_C) (top right), peripheral carbon dioxide sensitivity (G_P) (bottom left) and the ratio G_P/G_C (bottom right) for control and tramadol experiments. Each subject is represented by the same symbol in all diagrams.

1, which shows decreases in the fast and slow components ($\dot{V}_P$ and $\dot{V}_C$) after tramadol.

The estimated model parameters are collected in Table 1. Tramadol had no effect on the position of the $\dot{V}CO_2$ response curve relative to the *x*-axis (parameter B), but reduced the slope of the curve (i.e. the total carbon dioxide sensitivity) by 29 (20) (11–51)%. This was caused by a reduction in central and peripheral carbon dioxide sensitivities, by 30 (22) (15–54)% and 23 (46) (3–54)% respectively. Tramadol did not affect the ratio G_P/G_C. The trend term and the time constants and time delays of both chemoreflex loops were not affected (data not shown). In Fig. 2 the mean values of B, G_P, G_C and G_P/G_C of each subject for the control and tramadol experiments are shown in scatter diagrams.

Carbon dioxide output decreased significantly by a small amount [$\dot{V}CO_2$, control 0.19 (0.04) (0.15–0.22), tramadol 0.17 (0.04) (0.13–0.21) litre min^{-1} ($P<0.043$)]. The oxygen consumption and gas exchange ratio remained unaffected by tramadol [$\dot{V}O_2$, control 0.22 (0.06) (015–0.26), tramadol 0.21 (0.04) (0.20–0.24) litre min^{-1} (not significant); gas exchange ratio, control 0.89 (0.18) (0.93–1.03), tramadol 0.82 (0.11) (0.69–0.94) (not significant)].

Tramadol did not effect the arousal level of the subjects as judged by the BIS of the EEG [control 96.2 (0.6) (95.8–96.9), tramadol 94.7 (4.1) (91.3–97) (not significant)].

Two subjects reported side-effects several hours after taking tramadol. One reported dizziness, the other nausea and vomiting.

Discussion

We found that an analgesic dose of tramadol depresses respiration in healthy volunteers. Respiratory control was assessed by measuring the ventilatory response to carbon dioxide. The $\dot{V}E$–CO_2 response curve (i.e. its slope and its position relative to the *x*-axis) is a sensitive tool to assess the effects of pharmacological agents on ventilatory control and is superior to single measurements of $\dot{V}E$, arterial, end-tidal or transcutaneous PCO_2. Tramadol reduced the ventilatory carbon dioxide sensitivity by ~30%. This effect could be caused at various sites: the peripheral or central chemoreceptors, the integrating respiratory centres in the brainstem, the neuromechanical link between the brainstem and ventilation (i.e. motor neurone, neuromuscular junction, respiratory muscles and lung tissue) or sites involved in the control of behavioural state. Our approach of using the dynamic end-tidal forcing technique,[9 10] which allows us to quantify the relative contributions of the peripheral and central chemoreflex loops to total ventilation, in combination with measurement of the bispectral index of the EEG (an objective measure of sedation/hypnosis)[16] during the experiments enabled us to differentiate between these sites and give an approximate location of tramadol's respiratory sites of actions. Tramadol did not materially affect $\dot{V}O_2$, $\dot{V}CO_2$ or BIS, suggesting that tramadol did not depress carbon dioxide sensitivity by a decrease in the metabolic or arousal state of the subjects. An effect at sites common to both chemoreflex loops seems most probable because the outputs of the peripheral and central chemoreflex loops were decreased by about 25–30%. Tramadol probably affected the ventilatory control system by acting at the respiratory integrating centres within the brainstem. In this respect, tramadol does not differ from other agents acting at μ-opioid receptors.

We performed control and drug experiments on one day. For each subject, the order of experiments was the same: first the control and then the tramadol experiment. There are several reasons for this approach. We did not want to perform control and drug experiments on separate days, because day-to-day variability of the ventilatory responses to hypercapnia is more significant than within-day variability.[17 18] A randomized cross-over study on one day leads to excessively long sessions and discomfort of the subjects. Furthermore, because tramadol is not eliminated completely within a short time, an influence on subsequent control experiments cannot be excluded.[19] Because the differences between treatments could have been small, we opted to use a protocol in which the run-to-run variability was minimal.

Previous studies on the effect of tramadol on ventilatory control give conflicting results, which we relate to the various methods used to measure ventilatory effect and/or to the complexity of protocols. For example, Tarkkila and colleagues[3] and Vickers and colleagues[6] compared the respiratory effects of tramadol with meperidine or morphine on ventilation in anaesthetized patients breathing 0.3–1% halothane in 70% nitrous oxide before elective surgery. While meperidine and morphine caused significant respiratory depression, as observed by an increase in end-tidal PCO_2, and decreases in minute ventilation and respiratory rate, i.v. tramadol seemed devoid of respiratory effects or had only a minor effect on respiratory rate. Such studies are hard to interpret, taking into account the respiratory effects of halothane (depression of peripheral and central carbon dioxide responses[13 20]) and nitrous oxide, which can stimulate ventilatory control, probably as a result of its sympathicomimetic properties.[21] Interaction of these agents with the opioid and non-opioid actions of tramadol cannot be excluded.

Our observations support those of Seitz and colleagues, who found that the $\dot{V}E$–CO_2 response was depressed dose-dependently by 15–25% by tramadol 1 and 1.5 mg kg^{-1} i.v. in healthy awake volunteers.[5] Warren and colleagues tested the effect of oral tramadol on the ventilatory response to short-term (7 min) hypoxia against the background of mild isohypercapnia.[4] Whereas hypercapnic ventilation was reduced, an observation in agreement with our findings, tramadol had no effect on the hypoxic $\dot{V}E$ response. This is surprising in view of our present observation of a depressant effect of tramadol on respiration, which is probably located in the respiratory integrating centres. The ventilatory response to hypoxia is biphasic: an initial hyperventilatory response, originating in the carotid bodies, is followed after 3–5 min by a slow decline, which originates centrally (i.e. within the central nervous system).[22] The mechanism of this respiratory effect of central hypoxia remains unknown but may involve various neuromodulators. Tramadol may have reduced central hypoxic depression by its non-opioid modes of action, such as central serotonin release (see below), and thus offset the depression of the acute hypoxic response.

Tramadol and the *O*-desmethyltramadol metabolite of its (+) enantiomer produce analgesia by an agonistic effect on the μ-opioid receptor.[23] However, the antinociceptive effect of tramadol in the rat hotplate test is only partially antagonized by naloxone, and activation of opioid receptors appears to be responsible for only 50% of tramadol's analgesic effect.[1] The remainder of its analgesic action may be by inhibition of norepinephrine and serotonin reuptake and by facilitation of serotonin release in descending neural antinociceptive pathways.[1 24] The molecular mechanisms of the respiratory effects of tramadol remain unknown. Whereas the activation of the μ-opioid receptor is associated with respiratory depression,[25] the effects of monoamines on respiration are less evident.[26–28] Central release of serotonin may depress as well as stimulate breathing, depending on the type of respiratory neurone and 5-HT receptor subtype involved.[26] Most studies indicate that central release of norepinephrine causes respiratory depression.[27] To determine the relative effect of the μ-opioid receptor in tramadol-induced respiratory depression, Teppema and colleagues determined the ability of naloxone to reverse the depression by tramadol of the $\dot{V}_E$–CO_2 response in an anaesthetized cat model.[29] Respiratory depression by tramadol was reduced by 70–80% after naloxone pretreatment, suggesting that at least 70% of tramadol's respiratory effect is related to its action at opioid receptors, while the remainder could be by inhibition of serotonin and norepinephrine reuptake.

Respiration in perioperative patients is related to the balance between stimulation from pain, stress and activated chemoreflexes and depression resulting from sedation and the direct effect of analgesics and anaesthetics on respiratory neurones.[30] Our subjects were free of pain or surgical stress, which should be considered before extrapolating our findings to perioperative patients. The respiratory effects in the present study may have been overestimated. The effect observed in this study is equivalent to that found after morphine 0.13 mg kg^{-1} i.v. in healthy volunteers without pain.[12]

In conclusion, tramadol reduces the hypercapnic ventilatory response. This depression probably acts through the respiratory integrating centres within the brainstem.

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No clinical evidence of acute opioid tolerance after remifentanil-based anaesthesia

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We have prospectively assessed whether remifentanil-based anaesthesia is associated with clinically relevant acute opioid tolerance, expressed as greater postoperative pain scores or morphine consumption. Sixty patients undergoing elective gynaecological, non-laparoscopic, surgery were randomly assigned to receive remifentanil (group R, n=30) or sevoflurane (group S, n=30) based anaesthesia. Postoperative analgesia was provided with morphine through a patient-controlled infusion device. Mean (SD) remifentanil infusion rate in group R was 0.23 (0.10) $\mu g\ kg^{-1}\ min^{-1}$ and mean inspired fraction of sevoflurane in group S was 1.75 (0.70)%. Mean (SD) cumulative morphine consumption during the first 24 postoperative hours was similar between groups: 28.0 (14.2) mg (group R) *vs* 28.6 (12.4) mg (group S). Pain scores, were also similar between groups during this period. These data do not support the development of acute opioid tolerance after remifentanil-based anaesthesia in this type of surgery.

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One of the main problems of remifentanil-based anaesthesia is the rapid disappearance of analgesia after cessation of its infusion. As a result, a preventive analgesic approach with intraoperative i.v. administration of longer acting opioids is frequently used.[1] Nonetheless, large doses of intraoperative morphine or fentanyl in major abdominal surgery under remifentanil-based anaesthesia have failed to provide entirely adequate analgesia.[2 3]

It has been demonstrated that development of acute opioid tolerance to the analgesic effect of opioids occurs in animals.[4–7] However, the occurrence of this phenomena in humans is controversial,[8 9] and even more its clinical relevance.[10 11] The objective of this study was to determine whether remifentanil-based anaesthesia is associated with clinically relevant acute opioid tolerance, expressed as greater postoperative pain scores or morphine consumption, when compared with sevoflurane-based anaesthesia.

Methods

With the approval of the School of Medicine Ethics Committee, we prospectively studied 60 un-premedicated women (ASA I–II, 20–60 yr) undergoing elective gynaecological, non-laparoscopic, surgery. Exclusion criteria included a history of chronic pain, drug abuse, psychiatric disease, obesity (body mass index >30), and the intake of any analgesic drug within 48 h before surgery.

In the operating room before induction of anaesthesia, patients were instructed on how to use the patient-controlled analgesia (PCA) device and the visual analogue scale (VAS) (0=no pain; 100=worst possible pain). The average of three consecutive (5-min interval) non-invasive arterial pressure (NIBP) measurements was considered as the basal value. After standard monitoring (ECG, pulse oximeter, NIBP), anaesthesia was induced with fentanyl 3 $\mu g\ kg^{-1}$, propofol 2 $mg\ kg^{-1}$, rocuronium 0.6 $mg\ kg^{-1}$, and 2% sevoflurane. The trachea was then intubated. Then, patients were assigned to one of two groups by a table of random numbers generated with the StatView statistical software package. Patients in group R (remifentanil-based anaesthesia) were initially maintained with 0.5% sevoflurane inspired fraction, 50% nitrous oxide in oxygen (4 litres min^{-1}) and remifentanil 0.25 $\mu g\ kg^{-1}\ min^{-1}$. Patients in group S (sevoflurane-based anaesthesia) were initially maintained with 2% sevoflurane inspired fraction and 50% nitrous oxide in oxygen (4 litres min^{-1}). Arterial pressure was measured every 2.5 min. Increments or decrements of 0.05–0.1 $\mu g\ kg^{-1}\ min^{-1}$ of remifentanil (group R, n=30) and 0.5–1.0% sevoflurane (group S, n=30) were administered in order to maintain mean arterial pressure within 20% of basal values. All

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patients were mechanically ventilated to maintain end tidal carbon dioxide 30–35 mm Hg. Rocuronium 5 mg bolus was given to maintain one or two responses of the adductor pollicis to train-of-four stimulation. Administration of atropine, ephedrine and i.v. fluid administration was left to the anaesthetist's discretion. Neostigmine 1–3 mg and atropine 0.5–1.5 mg were administered at the end of surgery to antagonize residual neuromuscular block, if required. The anaesthetist was not blinded to group assignment.

All patients were extubated in the operating room and transferred to the recovery unit, breathing room air. Postoperative pain was assessed and managed by the staff of the pain service of our hospital (blinded to group assignment). Dynamic pain VAS pain scores were assessed by asking patients to cough in the supine position at 0, 15, 30, 45, 60, 90, 120 min and 24 h after arrival in the recovery unit. Initially, morphine 3 mg bolus doses were given intravenously until VAS pain scores were <50 mm and then the PCA system was connected (bolus dose morphine 1 mg and droperidol 0.2 mg; 8 min lockout). The following postoperative complications were recorded: nausea and vomiting, sedation (evaluated with a four point rating scale: 0=fully awake; 1=somnolent, responsive to verbal commands; 2=somnolent, responsive to tactile stimulation; and 3=asleep, responsive to painful stimulation), hypoxaemia (pulse oximeter saturation <90%, breathing room air), and respiratory depression (ventilatory frequency <10 min^{-1}). Nausea and vomiting were treated with ondansetron 4 mg i.v. Hypoxaemia was treated with 35% oxygen administered by mask.

Patient satisfaction with anaesthesia and pain management was assessed 24 h after surgery with a four point rating scale (1=very satisfied; 2=satisfied; 3=unsatisfied; 4=very unsatisfied).

Mean sevoflurane requirements for each patient were estimated from the vaporizer setting, which was recorded every 15 min. Mean remifentanil requirements were calculated by dividing the total amount of remifentanil infused (mg) by duration of anaesthesia (min) and weight (kg) for each patient.

The sample size was estimated to demonstrate a difference of at least 30% in morphine consumption (based on data of morphine consumption in this type of surgery obtained by the pain service of our hospital) with β=0.90 and α=0.05. The chi-squared and the unpaired Student's *t*-tests were used to study the homogeneity of general data. Two-way ANOVA was used to compare morphine consumption and VAS scores, and Mann–Whitney *U*-test to compare sedation and satisfaction. The level of statistical significance was set at P<0.05. All analyses were performed using the StatView statistical software package.

Results

All 60 patients completed the 24-h study. Patient characteristics and intraoperative data were similar in both groups (Table 1). Plasma creatinine concentrations were within normal limits in all patients. Seven well-controlled hypertensive patients were included in our study. Four patients in group S (two atenolol and two nifedipine) and three patients in group R (two enalapril and one atenolol). All these drugs were continued until the day of surgery. No patient required ephedrine and atropine only was used at the end of surgery after neostigmine administration for reversal of neuromuscular block. Mean (SD) remifentanil infusion rate in group R was 0.23 (0.1) µg kg^{-1} min^{-1}, and mean sevoflurane inspired fraction in group S was 1.75 (0.7)%. Before the PCA device was connected, morphine loading dose for group S was 11.9 (5.9) and for group R 13.7 (6.6) (NS). There were no differences between groups in pain scores (Fig. 1) and morphine consumption (Fig. 2) during the first 24 postoperative hours. In group R, 21 patients (70%) complained of nausea during the first 6 postoperative hours compared with 13 (43%) in group S (P<0.05). No

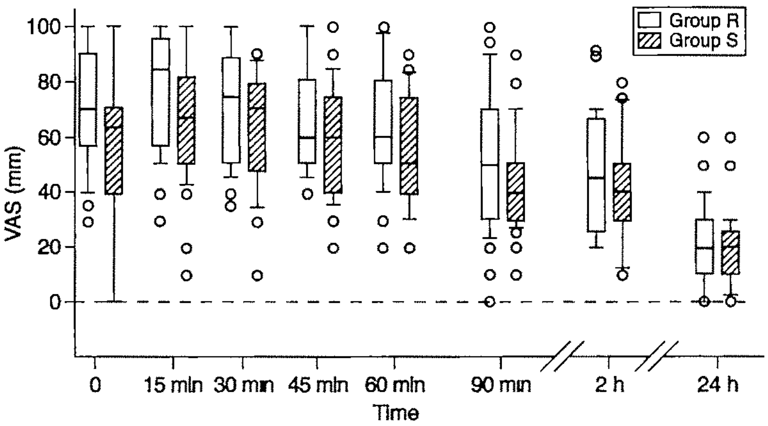

Fig 1 Box plots of the pain scores during the first 24 postoperative hours, for group R and S. The horizontal lines of each box represent the medians and quartiles The top and bottom of the vertical lines specify the 90th and 10th percentile, respectively. Scores above and below the vertical lines are plotted with circles. No statistically significant difference was noted between groups (P=0.14) ANOVA for repeated measures was used.

differences were found with respect to nausea and vomiting during the period 0–24 h (Table 2). Seven (23%) patients in group S and eight (27%) in group R suffered hypoxaemia during the first 2 postoperative hours (NS) and all responded favourably to 35% oxygen. No patient had a ventilatory frequency <10 min^{-1}. No significant differences were found between groups with respect to sedation scores and level of satisfaction (Table 3).

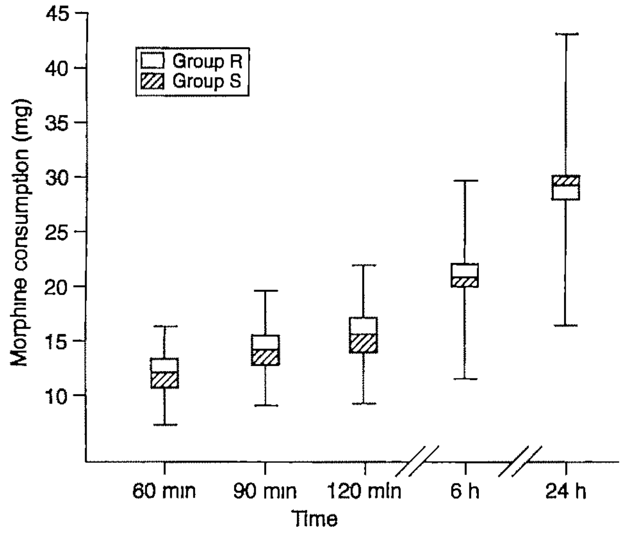

Fig 2 Cumulative morphine consumption in mg (mean (SD)), during the first 24 postoperative hours No statistically significant difference was noted between groups (P=0.6). ANOVA for repeated measures was used Group R=remifentanil-based anaesthesia, group S=sevoflurane-based anaesthesia

Table 1 Patients and surgical characteristics *Values are mean (SD) H/T/O=hysterectomy, tumour resection, and other. There were no significant differences between groups

	Group R (n=30)	Group S (n=30)
Age (yr)*	45 (8)	44 (9)
Weight (kg)*	67 (12)	65 (13)
Height (cm)*	158 (7)	160 (7)
ASA (I/II)	(7/23)	(12/18)
Type of surgery (H/T/O)	(24/3/3)	(17/7/6)
Duration of surgery (min)*	98 (45)	96 (37)
Duration of anaesthesia (min)*	116 (34)	118 (40)

Table 2 Incidence of nausea and vomiting

	Group R (n/%)	Group S (n/%)	P value
0–6 h			
Nausea	21/70	13/43	0.037
Vomiting	6/20	6/20	
0–24 h			
Nausea	21/70	14/47	0.06
Vomiting	7/23	7/23	

Table 3 Patient satisfaction. There were no significant differences between groups

	Group R (n/%)	Group S (n/%)
Anaesthesia satisfaction		
Very satisfied	19/65	24/78
Satisfied	7/23	5/18
Unsatisfied	1/4	0/0
Very unsatisfied	2/8	1/4
Pain management satisfaction		
Very satisfied	22/73	23/75
Satisfied	7/23	6/21
Unsatisfied	1/4	1/4
Very unsatisfied	0/0	0/0

Discussion

These results show that remifentanil infusion during general anaesthesia in this type of surgery is not associated with clinically relevant evidence of acute opioid tolerance.

Some recent studies have suggested that acute opioid exposure to large doses of fentanyl[13] or remifentanil[10] during surgery can be associated with a clinically important tolerance effect to opioid analgesia, manifested by greater pain scores or opioid consumption during the postoperative period. Moreover, delayed hyperalgesia from opioid exposure has been proposed as another possible explanation for the apparently worse pain and greater opioid consumption.[10 14 15] Both acute opioid tolerance and delayed hyperalgesia seem to share some similar molecular mechanisms which involve the activation of excitatory glutamate receptors of the *N*-methyl-D-aspartate (NMDA) system in the central nervous system.[15 16] However, many other mechanisms and systems are probably involved in the development of opioid tolerance.[17]

Evidence is controversial in humans. Gustorff,[8] using electrical pain stimulation in a placebo-controlled volunteers study, did not find early tolerance during 3 h of 0.08 μg kg^{-1} min^{-1} remifentanil infusion. Nonetheless, Vinik and Kissin[9] showed in volunteers that the analgesic effect of remifentanil 0.1 μg kg^{-1} min^{-1} was maximum at 60–90 min and then progressively declined, reaching 25% of the peak value after 3 h of constant-rate infusion. The main weakness of this study was the lack of a control group to rule out a 'learning or customing' effect to painful stimulation. However, even though the study by Vinik and Kissin did not adequately reflect the complex perioperative clinical condition, anaesthesia duration might be a key factor influencing the development of acute opioid tolerance.[4] As a result, it could be that, in spite of the higher doses of remifentanil used in our study, longer anaesthesia might have led to the development of clinically significant acute opioid tolerance effect. This idea is reinforced by Guignard's study,[10] which showed, in patients who had received remifentanil-based anaesthesia for surgery averaging 4 h, their demand for morphine in the first 24 h was nearly twice that of those who received desflurane-based anaesthesia.

Intensity of pain might be another factor that can influence the appearance of acute opioid tolerance. Using two animal models (upper and lower abdominal surgery), Ho and colleagues[18] explored the effect of postoperative pain on the prevention of acute tolerance to morphine antinociception in rats. They found that both types of surgery were associated with significant attenuation of acute opioid tolerance after i.v. infusion of morphine when compared with a control group. Similar results have been found in other animal models.[19] In our study, patients of both groups had high pain scores during the first 2 postoperative hours and this could have precluded the appearance of a clinically detectable opioid tolerance effect.

In animals, higher doses of morphine are more likely to produce acute opioid tolerance than lower doses.[4] Thus, the slightly higher remifentanil infusion rate in Guignard's study compared with ours cannot be ruled out as an additional explanation for the different results between both studies. With respect to postoperative complications and patient satisfaction, both anaesthesia regimens seem to be equally good. The higher rates of nausea observed in group R need to be confirmed because we do not have a record of fluid and neostigmine administration to be sure that both groups are comparable in this regard.

There is still a lot to learn with respect to the occurrence of acute tolerance, delayed hyperalgesia and pre-emptive opioid effect, their molecular mechanisms, their interactions and their clinical relevance in the perioperative period. However, based on our results we can conclude that remifentanil-based anaesthesia in this type of surgery is not associated with greater postoperative pain scores or morphine requirements when compared with sevoflurane-based anaesthesia. Clinical evidence of acute opioid tolerance is not supported by our results.

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Transtracheal high frequency jet ventilation for endoscopic airway surgery: a multicentre study

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Serious complications during high frequency jet ventilation (HFJV) are rare and have been documented in animals and in case reports or short series of patients with a difficult airway. We report complications of transtracheal HFFJV in a prospective multicentre study of 643 patients having laryngoscopy or laryngeal laser surgery. A transtracheal catheter could not be inserted in two patients (0.3%). Subcutaneous emphysema (8.4%) was more frequent after multiple tracheal punctures. There were seven pneumothoraces (1%), two after laser damage to the injector, one after difficult laryngoscopy, four with no clear cause. Arterial desaturation of oxygen was more frequent during laser surgery and in overweight patients. Transtracheal ventilation from a ventilator with an automatic cut-off device is a reliable method for experienced users. Control of airway pressure does not prevent a low frequency of pneumothorax.

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Diagnostic or surgical laryngoscopy requires a method that can give good exposure of the larynx, continuous control of airway patency, and immobility of the vocal cords. Techniques suggested include spontaneous ventilation under light anaesthesia in adults or deep anaesthesia in children,[1] an apnoeic technique, especially in children,[2] intermittent positive pressure ventilation *via* a small microlaryngeal tube,[3] manual jet ventilation at a normal ventilatory frequency[4] or high frequency jet ventilation (HFJV).[5] Most require specific skills and equipment, which is why none have gained general acceptance. Jet ventilation has been an established anaesthetic technique of ventilation for surgical laryngoscopy for over 20 yr;[5] its main advantage is good access to the surgical field because of the small diameter of the transtracheal catheter, and the ability to maintain adequate ventilation throughout the procedure.[6] The method uses a metallic tube or a cannula placed either supraglottically (which may be attached to the endoscope) or subglottically (after intubation *via* the nasal or the oral route or after puncture of the cricothyroid membrane) at a normal rate or at high frequency. Transtracheal jet ventilation allows endoscopic surgical access to the larynx[7] and can be used for patients with acute airway problems.[8] Laryngoscopy and intubation are not needed, no apparatus is placed in the upper airway, and adequate gas exchange is obtained.[7] Serious complications during HFJV are rare. There are case reports or series of patients with complications[8] such as transtracheal catheter dysfunction[9] and barotrauma.[10] Expiratory obstruction and pulmonary hyperinflation may cause subcutaneous emphysema, pneumomediastinum and pneumothorax.[8] To avoid this problem, modern jet ventilators now have safety systems to stop inflation if tracheal pressure is too great.[11]

We assessed transtracheal jet ventilation (TTJV) during laryngoscopic and laser surgery procedures in a prospective multicentre study.

Methods

Three hospitals were studied over a 1-yr period after local ethical approval. After obtaining informed consent, patients about to undergo upper airway endoscopy were studied. We noted: age, weight, height, previous cervical radiotherapy, if skin fibrosis was present, chronic obstructive pulmonary disease (COPD) defined as asthma or productive cough over 3 consecutive months for at least 2 yr, and radiological evidence of pulmonary emphysema. Exclusion criteria were infection at the puncture site and coagulation disorders. Anaesthesia was induced with propofol (2 mg kg^{-1} i.v.) and

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alfentanil (15 μg kg^{-1}) and maintained with propofol infusion and intermittent doses of alfentanil. Muscle relaxation was achieved with either succinylcholine infusion or vecuronium bromide (0.05 mg kg^{-1}) antagonized with neostigmine and atropine, and monitored by nerve stimulator.

After induction of anaesthesia, a catheter was introduced through the cricothyroid membrane into the trachea, 13 or 14 gauge for adult patients and 18 gauge for children aged less than 3 yr. Two types of tracheal catheters were used: a Teflon 14-gauge, 10 cm length, arterial catheter (Seldicath® Plastimed, France) introduced using the Seldinger method[11] or a Ravussin 13-gauge catheter directly introduced into the trachea under endoscopic control by the surgeon (VBM Laboratory, Germany).[12] The number of punctures and the experience of the anaesthetist (consultant or resident) were recorded. In all cases, 2 ml of 2% lidocaine were injected through the injector. Taking into account the usual tracheal length, the distal tip of the injector was expected to be located between 2 and 4 cm above the carina. After induction, HFJV was started using the following settings: rate 2 Hz, inspiratory/expiratory ratio 0.5, driving pressure 2.8–4 bar according to age, weight and chest expansion, $F\text{I}_{O_2}$=1 except during laser surgery. The patients were not intubated and passive expiration was facilitated by manually lifting the jaw before and after laryngoscopy. Two HFJVs were used: the GR300 (LSSA, Fontenay sous bois, France) or the AMS 1000 (Acutronic medical systems, Hirzel, Switzerland). Both were equipped with a fail-safe system allowing the measurement of expiratory airway pressure through the transtracheal catheter.[11] Each end-expiratory pressure value was recorded by a microprocessor located in the ventilator. This microprocessor allowed the next inflation only when end-expiratory pressure was less than a preset value (usually 4 cm H_2O). This feature detects overinflation during laryngoscopy. Driving pressure was progressively decreased during emergence and HFJV was stopped when patients became conscious. Mechanical ventilation was restarted if breathing was inadequate. The tracheal catheter was withdrawn in the recovery room.

Duration of laryngoscopy, upper airway disease (benign or cancer), use of laser and episodes of desaturation (<90% for >1 min) were recorded. After the procedure, the surgeon graded the extent of upper airway obstruction by allocating a numerical score for each of the following features: tumour position, tumour infiltration, the severity of tumour vegetation, oedema, and fibrosis (Table 1). To summarize these values, two final scores were calculated, by addition and also by multiplication of the individual component values. Each of these values was used for comparisons.[7]

In the recovery room, Sp_{O_2} was measured and the use of supplementary oxygen, intubation or tracheotomy was recorded. If serious postoperative breathing difficulty was present, HFJV was added to spontaneous breathing until complete recovery or resolution of the obstruction.[13] Cervical subcutaneous emphysema was sought systematically by neck examination; when present, a chest x-ray was performed to diagnose pneumomediastinum or pneumothorax.

Results are expressed as mean (SD). Predictive factors were determined only in adult patients. Children were included in the assessment of complications but were excluded from statistical analysis because of the small number of patients and the different clinical context. Univariate non-parametric tests were first used, followed by stepwise multiple logistic regression which was used to examine the relationships between complications and perioperative data. The results were considered significant if $P<0.05$.

Results

There were 643 patients, 523 males and 120 females, and comprising 632 adults and 11 children (Table 2). A Seldicath® catheter was used in 579 cases and a Ravussin catheter in 64 cases. The complication rate was similar with both transtracheal catheters and did not depend on the experience of the anaesthetist.

The catheters were successfully inserted in 641 patients (99.7%) and could not be inserted in two patients (0.3%). Ninety-two per cent of insertions were successful at the first attempt, 6% at the second, 1.4% at the third and 0.6% at the fourth attempt. No catheter was misplaced or displaced and no bleeding was observed. Multiple punctures were more frequent (13%) in patients with previous cervical radiotherapy compared with 7% in patients without cervical radiotherapy ($P<0.05$). No complication was observed during laryngoscopy in children.

Table 1 Scoring of upper airway obstruction Two final scores were calculated by adding and multiplying each value A value of 1 was given to 'no tumour' when the score was calculated by multiplication

Category	Scoring value
Cancer localization	
No tumour	0
Tongue	1
Oropharynx	2
Base of tongue	3
Hypopharynx	4
Larynx	5
Infiltration	
No	1
Yes	2
Vegetations	
No	1
Mild	2
Major	3
Oedema	
No	1
Yes	2
Fibrosis	
No	1
Yes	2

Table 2 Patient details Mean (SD) [range]

	All patients (adults and children) (*n*=643)	Children (*n*=11)	Adults (*n*=632)
Age	54 (13) yr [1 month to 86 yr]	5.4 (5.0) yr [1 month to 13 yr]	55 (12) yr [17–86 yr]
Sex ratio M/F	523/120	3/8	520/112
Weight (kg)	66 (15) [3–120]	16.7 (13.5)	67 (14) [30–120]
Height (cm)			169 (8) [143–192]
COPD	15%	0%	16%
Radiological emphysema	8%	0%	8%
Cervical radiotherapy	21%	0%	21%
Cervical skin fibrosis	11%	0%	11%

Table 3 Factors associated with subcutaneous emphysema * Fisher exact *t*-test

	Without subcutaneous emphysema	With subcutaneous emphysema	
Duration (min)	21.5 (23.9)	26.6 (28.7)	NS
Obstruction score (additive)	0.16 (0.37)	0.21 (0.43)	NS
Obstruction score (multiplication)	10.5 (13.8)	13.9 (16.7)	NS
Weight (kg)	67.3 (13.5)	70.7 (18.5)	NS
Age (yr)	55.0 (14.8)	61.9 (14.4)	NS
Puncture attempts >2	10/581, 1.7%	4/49, 8.1%	*P*=0.02*

Subcutaneous emphysema was limited to the neck in 53 of 643 patients (8.4%) and extended to the face or the thorax in 14 patients(2%). Subcutaneous emphysema was more frequent after multiple tracheal punctures (2% after a single tracheal puncture and 8% after multiple punctures) (Table 3). Pneumomediastinum was diagnosed in 16 patients (2.5%) and was always associated with subcutaneous emphysema.

Seven pneumothoraces occurred in the first 24 h (Table 4). Because of the small number of patients, risk factors for a pneumothorax could not be determined by a stepwise analysis. In three patients, the pneumothorax was small and unilateral and did not necessitate any treatment before resolving spontaneously; no obvious cause was found. In four cases, pleural drainage was needed for 24–72 h. In three of these cases, the pneumothorax occurred during prolonged endoscopy for obstructive cancer; two were related to laser damage to the transtracheal catheter during laryngeal disobstruction in patients with tumours; the third pneumothorax occurred after a long and difficult laryngoscopy in a patient with a large tumour. The last pneumothorax occurred without any explanation.

Oxygen desaturation was more frequent when delivered oxygen concentration was less than 100% and during laser surgical procedures (*n*=25) (Table 5). Other factors predicting low Sp_{O_2} were multiple tracheal punctures and obesity. In one case, desaturation was caused by the tracheal catheter tip being located in a bronchus, recognized by chest auscultation. Urgent tracheotomy was never required.

Discussion

We found that HFJV, *via* a catheter placed through the cricothyroid membrane, is an easy and safe way to ventilate patients about to undergo ENT laryngoscopy, microlaryngoscopic, and laser surgery. The method offers the following advantages: no intubation, excellent surgical view of the larynx, and adequate oxygenation in most patients. Ventilation, or at least oxygenation, can be maintained throughout the procedure. HFJV overcomes the disadvantage of an anaesthetic technique using a tracheal tube which can hide the posterior part of the glottis and which carries the risk of fire in the airway.[14] Finally, HFJV is useful during recovery; at the end of the procedure, HFJV was tolerated by patients recovering from muscle paralysis and was continued until the patients fully recovered from anaesthesia. Leaving the catheter in the trachea during the early recovery period allows adequate emergency oxygenation at a time when re-intubation may be difficult or contraindicated.[6]

TTJV has been used routinely in our institutions for more than 10 yr and we have a large experience in this field. Transtracheal ventilation can be unsafe in unexperienced hands.[6] In a retrospective study of 58 hospitals, complications were more frequent when experience of jet ventilation was limited.[14] Potential problems exist and a good understanding of the technique is necessary.[8] Even when used for resuscitation, the anaesthetist should carry out transtracheal ventilation under supervision in a more controlled situation.[15]

The cricothyroid membrane is the route of choice for transtracheal ventilation as it has no blood vessels, with a low risk of bleeding.[16] The puncture can be done with general or local anaesthesia, or directly in emergency situations. It must be strictly in the midline to avoid misplacement. Passing a catheter through the infracricoid membrane should be avoided because of potential bleeding but can be done when the cricothyroid membrane cannot be punctured, for example if a surgical scar or subglottic tumour are present. Mucosal lesions related to laryngoscopy and intubation and inadvertent placement or migration of an injection catheter into the oesophagus can be avoided.[17] In patients with an abnormality of the upper airway, such as in cases of head and neck cancer, it can be valuable. In these

Table 4 Data for the seven pneumothorax cases

Time	Age (yr)	Weight (kg)	Puncture attempts	Obstruction score	Duration (min)	Associated complications	Mechanism	Treatment
Preoperative	55	80	4	40	90	Low Sa_{O_2}	Section catheter	Drainage
Preoperative	62	61	2	60	80	Low Sa_{O_2}	Section catheter	Drainage
Preoperative	43	61	1	20	120	0	Difficult laryngoscopy Airway obstruction	Drainage
Postoperative	66	70	1	1	7	0	Unknown	Drainage
Postoperative	31	80	1	1	10	0	Unknown	0
Postoperative	61	62	2	8	21	0	Unknown	0
Postoperative	64	71	1	12	15	0	Unknown	0

Table 5 Factors associated with oxygen desaturation (Mean (SD)). *Fisher exact *t*-test. Using multiple logistic regression, episodes of low-oxygen desaturation were more frequent during laser surgery when $F\text{I}_{O_2}$ was less than 1. Complications (pneumothorax, subcutaneous emphysema and low-oxygen saturation) were more frequent after difficult transtracheal puncture. A history of chronic bronchitis did not predict complications

	Without desaturation	With desaturation	
Duration (min)	20.8 (23.4)	42.9 (30.4)	NS
Obstruction score (multiplication)	10.5 (13.7)	13.9 (18.5)	NS
Weight (kg)	67.1 (13.6)	73.4 (12.2)	P=0.03
Age (yr)	54.9 (0.1–86)	58.8 (3–83)	NS
Puncture attempts >2	17/526; 3.2%	8/40, 20%	P=0.0001*
Laser surgery	15/526; 2.8%	10/75, 13.3%	P=0.0001*
$F\text{I}_{O_2}$=1	505/517, 97.6%	12/83; 14.5%	P=0.0008*
COPD	19/504, 3.8%	6/91; 6.6%	NS

patients, a TTJV catheter allows rapid induction and adequate control of the airway.[8]

Adverse events were infrequent and complications were mainly related to (1) the puncture itself, (2) mechanical problems (subcutaneous emphysema, pneumomediastinum and pneumothorax, (3) episodes of low-oxygen saturation, and (4) recovery.

The puncture

The failure rate of cricothyroid membrane puncture was small (0.3%). The number of complications was not influenced by the experience of the anaesthetist (junior *vs* senior) or the type of transtracheal catheter (Seldicath® or Ravussin catheter). Most of the puncture difficulties were related to abnormal anatomy, which is previous radiotherapy, and should be identifiable preoperatively. Conventional i.v. catheters are not safe for jet ventilation because they are short, thin-walled, and easily kinked. The use of metallic needles has been proposed but the risk of tracheal perforation during patient movements seems high.[18 19]

Mechanical problems

The major concern during jet ventilation is the risk of subcutaneous emphysema, pneumomediastinum, pneumothorax, and even pneumoperitoneum. Such complications have been reported after endotracheal intubation (0.04%), but with less incidence than after jet ventilation (0.2%).[14] They are related either to barotrauma or tracheal mucoseal trauma and have been reported in adults and children, using orotracheal, nasotracheal, or transtracheal catheters.[19] Subcutaneous cervical emphysema is more frequent after difficult tracheal puncture, especially in patients with previous cervical radiotherapy. The gas mixture enters the subcutaneous space around the puncture site. This is of no major clinical consequence, but patients, anaesthetist, and surgeon should be aware of this potential complication. Pneumomediastium may be related to the extension of the subcutaneous emphysema or to some damage to the tracheal mucosa. The Seldicath® catheter is relatively rigid and may hit the tracheal wall at the end of each insufflation, allowing a high-pressure gas mixture to penetrate the submucosal space. We report a 1% incidence of pneumothorax which is similar to normal rate jet ventilation.[4] Pneumothorax can occur despite the use of ventilators equipped with a system to control end-expiratory tracheal pressure. Few prospective studies have quantified this risk when using jet ventilation: two pneumothoraces were reported in a series of 318 patients using the jet insufflation technique via a foil wrapped catheter.[4] In our study, two bilateral pneumothoraces followed a laser impact on the catheter during laryngeal dis-obstruction. In this condition, transtracheal ventilation should be used very cautiously, and HFJV through a nasotracheal catheter could be a better method. In any case, the anaesthetist must check the position of the catheter endoscopically. A laser resistant tracheal tube may be an alternative method. This is less convenient for the surgeons, does not prevent the occurrence of pneumothorax completely and exposes the patient to the risk of tracheal tube fire.[14] In the remaining five cases, the pneumothoraces were small and were recognized in the recovery room. They were always associated with subcutaneous emphysema with no evidence of upper airway obstruction. Disruption of the perivisceral fascia can follow cricothyroid membrane puncture or a lesion to the tracheal wall at the injector tip. As we did not inspect the tracheal wall at the end of the laryngoscopy, we cannot be sure of this. Finally, a pneumothorax may be related to high-airway pressure during recovery (cough or active expiration). This could explain some complications diagnosed after endoscopy. End-expiratory pressure monitoring has been found to indicate tracheal pressure measured with a separate catheter in model lung studies and relate to change in pulmonary volume in patients during laryngoscopy.[11] Although barotrauma may be related to excessive peak airway pressure, we used end-expiratory pressure because of technical constraints. As pressure changes are small during TTJV,[20] this difference was neglected.

Episodes of low-oxygen saturation

During HFJV, oxygenation depends upon several factors:[21] the injected oxygen concentration, the ratio of entrained gas, and the increase in functional respiratory capacity (PEEP effect). Inspired gas is a mixture of injected gas and entrained air. Entrained air is limited during transtracheal HFJV,[22 23] so $F\text{I}_{O_2}$ was high and oxygenation was always adequate during laryngoscopic and microsurgical procedures. Episodes of oxygen desaturation were more frequent during laser surgery when $F\text{I}_{O_2}$ was decreased (the use of $F\text{I}_{O_2}$ greater than 0.4 is contraindicated during laser surgery[24 25]). In most of these patients, it was necessary to stop laser surgery during short periods of time in order to increase $F\text{I}_{O_2}$. In two patients, hypoxic episodes were related to bilateral pneumothorax, and tracheal intubation was required before pleural drainage. One case of oxygen desaturation was caused by the cricothyroid catheter lying in the right main bronchus; this complication should be detected by systematic pulmonary auscultation. Carbon dioxide retention can occur during jet ventilation, particularly in COPD and obese patients. Blood gas analysis was not performed in our study but it is likely that some patients were hypercapnic. To provide non-invasive ventilation monitoring during laryngoscopy, tracheal gas can be aspirated through the injector after stopping the ventilator. This allows the diagnosis of hypo- or hyperventilation.[26] Obesity is considered a risk factor for hypoxaemia during conventional ventilation and HFJV[7] and our data support this. A low Pa_{O_2} has also been reported in COPD patients under HFJV,[7] but we did not confirm this observation.

Recovery

Upper airway obstruction is common after direct laryngoscopy. This complication was not quantified in our study because of the difficulty in assessing the level of obstruction. Emergency tracheotomy or reintubation was never indicated in this large group of patients partially because of the use of short-acting anaesthetics and reversal of neuromuscular blocking agents. The catheter was left in place and withdrawn before the patient returned to the ward, so that immediate reventilation and/or oxygenation were possible. As patients were not intubated, weaning from the ventilator was easy to achieve by decreasing the driving pressure before stopping jet ventilation. Low-pressure (<2 bar) HFJV may be restarted and superimposed on spontaneous breathing in a conscious or semi-conscious patient; if expiration is easy, the risk of barotrauma is limited and this method can be used even in patients with severe upper airway obstruction.[13] TTJV is an attractive alternative to tracheotomy in this difficult situation.[27]

Specific methods have been developed to prevent fire, such as foil-tape and saline-soaked pledgets protected tubes or special tubes designed to resist a laser beam.[24–30] A transtracheal catheter can be touched by the laser beam but its low flammability (Teflon) reduces the risk of fire with this technique.[28] Its cost is less than that of the special tubes designed to resist a laser. Finally, perfect surgical conditions need an immobile field, with no vocal cord movement. In case of abnormal forced movements of vocal folds or any other cause of obstruction, jet ventilation can be stopped transiently during laser treatment (apneic oxygenation).

As vapourisers are not available on jet ventilators, total i.v. anaesthesia was used in all cases. Propofol provides satisfactory conditions[31] and muscle relaxation was added to prevent any movement of the vocal cords. Awareness was not encountered in our study, probably because propofol was supplemented with opiates.[32]

Conclusion

HFJV delivered by a ventilator with an automatic cut-off device is a reliable technique in the hands of trained personnel, used for laryngoscopy and laser surgery in a large series of patients. The risk of subcutaneous emphysema and pneumothorax, despite automatic control of airway pressure, is present. Anaesthesia and ventilation may be achieved despite the lesion and the surgical manoeuvres. Return to spontaneous breathing is particularly easy to control.

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Tracheal tube pressure change during magnetic stimulation of the phrenic nerves as an indicator of diaphragm strength on the intensive care unit

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Diaphragm strength can be assessed from twitch gastric (TwPgas), twitch oesophageal (TwPoes), and twitch transdiaphragmatic pressure (TwPdi) in response to phrenic nerve stimulation. This requires the passage of balloon catheters, which may be difficult. Changes in pressure measured at the mouth during phrenic nerve stimulation avoid the need for balloon catheters. We hypothesized that pressures measured at the tracheal tube during phrenic stimulation, could also reflect oesophageal pressure change as a result of isolated diaphragmatic contraction and, therefore, reflect diaphragm strength. We aimed to establish the relationship between twitch tracheal tube pressure (TwPet), TwPoes, and TwPdi in patients in the supine and sitting positions. The phrenic nerves were stimulated magnetically bilaterally, in 14 ICU patients while supine and on another occasion while sitting up at 45°. In the sitting position mean TwPoes was 9.1 cm H_2O and TwPet 11.3 cm H_2O (mean(SD) difference –2.2 (SD 1.5)). In the supine position mean TwPoes was 8.1 cm H_2O and TwPet 9.9 cm H_2O (mean difference –1.8 (2.2)). The difference between TwPoes and TwPet was less at low twitch amplitude; less than ±1 cm H_2O below a mean twitch height of 8 cm H_2O supine and 10 cm H_2O sitting. Sitting TwPet was related to TwPoes r^2=0.93 and TwPdi r^2=0.65 (P<0.01). Supine TwPet was related to TwPoes r^2=0.84 and TwPdi r^2=0.83 (P<0.01). The mean within occasion coefficient of variation while sitting was TwPet=13.3%, TwPoes=13.9%, TwPdi=11.2%, and supine TwPet=11.6%, TwPoes=14.6%, TwPdi=11.8%. We conclude that TwPet reflects TwPoes during diaphragmatic stimulation and is worthy of further study to establish its place as a guide to the presence of respiratory muscle strength and fatigue.

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The assessment of diaphragm strength on the intensive care unit (ICU) is difficult whether the pressures are recorded during a maximal voluntary effort or a single twitch stimulation of the phrenic nerves. Volitional tests rely on the cooperation of the patient, so measurements may not be possible on the ICU or may underestimate respiratory muscle strength because of the effects of sedation even when using the semivolitional modification by Marini,[1] of the maximal inspiratory mouth pressure technique.[2]

Conventionally, balloon catheters are passed into the oesophagus and stomach to measure pressure above and below the diaphragm. The difference between these two pressures is transdiaphragmatic pressure, which is an index of diaphragmatic strength during phrenic nerve stimulation.[3 4] However, the requirement for balloon catheters makes these methods invasive. The oesophageal and gastric balloon are difficult to position and the measurement is subject to artefact, especially when supine and in the presence of atelectasis. A means of gauging mean pleural or

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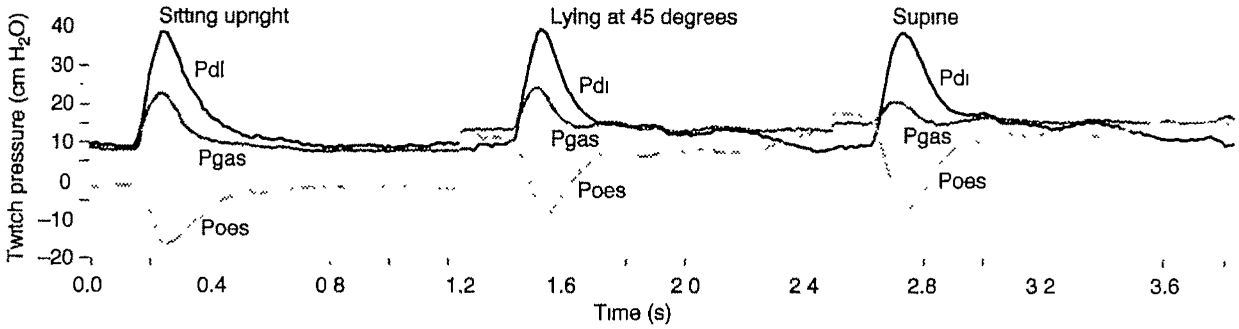

Fig 1 Twitch pressure traces sitting upright, lying at 45° and supine, showing the change in relative size of TwPoes and TwPgas in relation to posture

oesophageal pressure change in response to diaphragmatic contraction, by measuring airway or tracheal tube pressure, would facilitate the assessment of diaphragm strength on the ICU.

Pressures measured at the mouth during phrenic nerve stimulation (twitch mouth pressure) have already been used in ambulant patients with electrical and cervical magnetic stimulation,[5 6] although glottic closure can be a problem when mouth pressures are compared with twitch oesophageal pressure (TwPoes). This would not be a problem in the intubated patient, when twitch tracheal tube pressure (TwPet) is measured.

Non-volitional tests of diaphragm strength conventionally require electrical stimulation of the phrenic nerves. However, the adequacy and consistency of stimulation may be a problem because of the need to position the stimulating electrodes precisely over the nerves.[7] The technique of bilateral anterolateral magnetic stimulation (BAMPS) over the surface markings of the phrenic nerves in the neck, allows supramaximal bilateral phrenic stimulation in supine patients, without the need for neck flexion, which is required with the cervical approach.[8] This produces a pattern of stimulation very similar to bilateral electrical stimulation (BES).[9 10]

Therefore, if the BAMPS technique could be combined with TwPet measurements, this would provide a non-volitional and non-invasive assessment of diaphragm strength on the ICU. These recordings would allow us to assess more readily diaphragmatic strength in the ventilated patient and so help the complex assessment of the balance between the capacity of the respiratory system and the load placed upon it, particularly during weaning from respiratory support.

However, even though posture has little effect on TwPdi it does affect the ratio of the decrease in oesophageal pressure to the increase in gastric pressure that make up the change in transdiaphragmatic pressure.[9 11] For example, when the diaphragm is stimulated to contract in the supine position there is a larger decrease in twitch oesophageal pressure (TwPoes) than when sitting, but a relatively smaller contribution from the increase in gastric pressure (TwPgas), so overall twitch transdiaphragmatic pressure (TwPdi) is little affected by posture (Fig. 1).[11] Therefore, it was necessary to assess our new technique in both the supine position, when the oesophageal pressure contribution to changes in TwPdi would be high, and in the sitting poition where the gastric component, which would not be measured by twitch tracheal tube pressure (TwPet), would be greater, to determine if a useful relationship between TwPet and TwPes or TwPet and TwPdi could be established in the two postures.

The TwPoes/TwPgas ratio depends on posture, on lung volume, and also varies from individual to individual. However, providing posture and volume are constant TwPoes/TwPgas or TwPoes/TwPdi are constant within individuals.[12] Therefore, within an individual, changes in TwPet reflect TwPoes. A certain percentage change in TwPet would reflect the same change in TwPdi, even without knowing TwPgas. The technique may be useful in longitudinal studies and screening for major weakness, even if absolute values for TwPdi are not possible. This could prove very useful as repeated insertion of balloon catheters often proves too invasive and difficult.

We therefore aimed to measure twitch TwPet proximal to an occluded tracheal tube, during BAMPS in the supine and sitting position, to determine whether this reliably reflected oesophageal pressure change during diaphragmatic contraction and could, therefore, act as an indicator of TwPdi in intubated patients.[13]

Methods

Study population

Fourteen consecutive patients (four female and 10 male) mean age 58 yr (range 45–71), who had undergone coronary artery bypass surgery were studied during the first 12 h after admission to the ICU. None had any neurological disease or diabetes. Patients with pacemakers or temporary pacing wires were excluded; however, patients with central lines were not. None had pre-existing symptoms or signs of lung disease, although formal lung function testing was not undertaken. The study was approved by the local ethics committee and all patients gave informed written consent.

Measurements

Pressure measurements were made from oesophageal and gastric balloon catheters[14] (PK Morgan, Rainham, Kent, UK), passed through the nose shortly after induction of anaesthesia via a long uncuffed red rubber nasotracheal tube, which had been passed into the oesophagus and then removed once the balloons were in place. Appropriate positioning of the balloons was initially confirmed using the technique of Ducros.[15] Later, once spontaneous breathing had been resumed, the position of the balloons was once more confirmed by occluding the tracheal tube and asking the patient to make a gentle inspiratory effort;[16] if the balloons were correctly positioned the change in tracheal tube pressure equalled the change in Poes. Pressure measurements were also made from the proximal end of the tracheal tube via a catheter of similar material, length, and diameter as the balloon catheter tubing.

Phrenic nerve stimulation

The phrenic nerves were stimulated with two 43-mm mean diameter double coils placed anterolaterally on the neck over the phrenic nerves. Each double coil was powered by a Magstim 200HP stimulator (The Magstim Company, Whitland, Dyfed, Wales, UK). The stimulators were charged to 100% of maximum power and triggered simultaneously. This level of power output is known to produce stimulation which is supramaximal or very close to being so.[9]

Changes in lung volume alter the position of the inspiratory muscles and so influence apparent diaphragm strength. For example, at high lung volumes the diaphragm is flattened, so reducing its ability to generate negative intrathoracic pressures during a maximal contraction. On the other hand, reductions in lung volume increase the curvature of the diaphragm and increase its ability to generate inspiratory pressures,[17 18] but are associated with atelectasis and worsened compliance.

The effect of potentiation may confuse diaphragm strength measurements. A fully potentiated twitch is 50% larger than a twitch in the same subject when fully rested.[19 20] This makes exact comparisons of strength more difficult to interpret unless patients can be rested for 20 min, avoiding all vigorous respiratory efforts before testing. On the ICU this could be achieved by providing adequate respiratory support.

Study design

To minimize potentiation,[19 20] all subjects were observed for 20 min to ensure that no vigorous respiratory efforts were made. Potentiation is the phenomenon whereby twitch amplitude depends on the recent contractile history of the muscle. Providing a muscle has not worked so hard that it is fatigued, a recent maximal voluntary contraction will temporarily alter the behaviour of the muscle so that it produces a twitch up to 50% greater than normal amplitude in response to a single twitch stimulation. This effect lasts for 20 min. Manipulations involving the tracheal tube were made as gently as possible to avoid stimulating the airway, which might lead to contractions that could potentiate the diaphragm. Then the tracheal tube was momentarily occluded and the phrenic nerves stimulated. Stimulations were made at end-expiration and before the next inspiration during mechanical ventilation. Those subjects who were spontaneously breathing on the tracheal tube via a T piece, were asked to breath in time with instructions and then relax at the end-expiratory position. The tracheal tube was then occluded and the phrenic nerves stimulated. On each occasion five stimulations were made.

Therefore, two sets of measurements were made on separate occasions in each patient; in a supine position and with the patient sitting. There is evidence to suggest that diaphragm strength can be expected to fluctuate in the postoperative period after coronary artery surgery.[21] Therefore, no attempt was made to directly compare measurements made in the supine and sitting up positions.[21] Instead the aim was to determine if TwPet could be a useful indicator of TwPoes and hence TwPdi in either position. In addition, changes in lung volume have been shown to affect TwPoes more than TwPgas and so the relationship between TwPet, TwPoes, and TwPdi could also change over the same time period.[18] However, it was possible to attempt to determine if a linear relationship existed between TwPet, TwPoes, and TwPdi in each of the two different positions.

The pressure traces were rejected if the baseline oesophageal or gastric pressure was distorted or if the twitch was imposed on a spontaneous or mechanical breath. The stimulations were 1 min apart. A small ramp of stimulations was made before the recordings to confirm that the stimulations were supramaximal or close to supramaximal.

Signal processing

Pressures were recorded via identical Validyne MP45 transducers (response range ±150 cm H_2O) and amplified by Validyne carrier amplifiers (Validyne Corporation, Northridge, CA, USA). These were calibrated before each study with a Universal Pressure Meter (Bio-Tek Instruments Inc., USA), which was regularly checked for accuracy with a water manometer.[22] The signals were passed to a 12-bit NB-MIO-16 analogue to digital converter board (National Instruments (NI), Austin, TX, USA), which had been installed within a MacIntosh Centris 650 computer (Apple Computer Inc., Cupertino, CA, USA). Pressure traces were analysed using programs based on LabView 2.2 software (NI).

Data collection

Pressure traces were inspected on line during the stimulation procedures to ensure they began on a steady baseline pressure at end-expiration. Twenty-two pressure traces were deemed unsatisfactory on subsequent off-line analysis and so excluded from the study (11 in the sitting position and 11 supine). Therefore, a total of 118 pressure traces out of a possible 140, all demonstrating Pet, Poes, Pgas, and Pdi in a total of 14 patients, were included in the analysis.

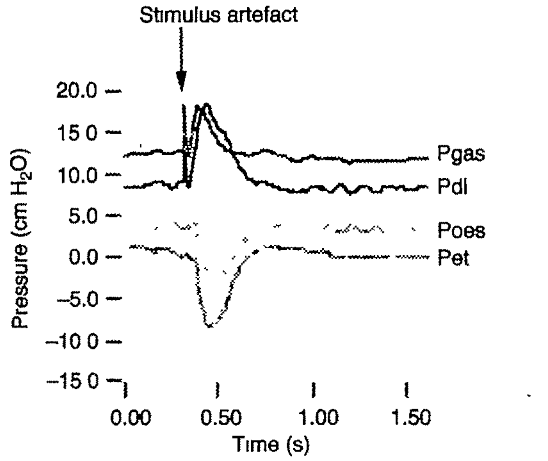

Fig 2 Pressure responses to BAMPS in a supine patient on the ICU. Irregularities in the oesphageal pressure wave are a result of cardiac artefacts

Statistical analysis

The statistical analysis was performed using Statview 4 (Abacus Concepts Inc., Berkley, CA, USA), and included linear regression, Wilcoxon Sign Rank tests and Bland and Altman plots.[23]

To allow a comparison of the ratios between TwPet, TwPoes, and TwPdi linear regression was used. The regression equations were also calculated with 'no intercepts', that is, made to pass through the zero point on both axes to allow the ratio between the variable on the ordinate and the abscissa to be calculated. Wilcoxon Sign Rank tests were used to compare TwPoes and TwPet.

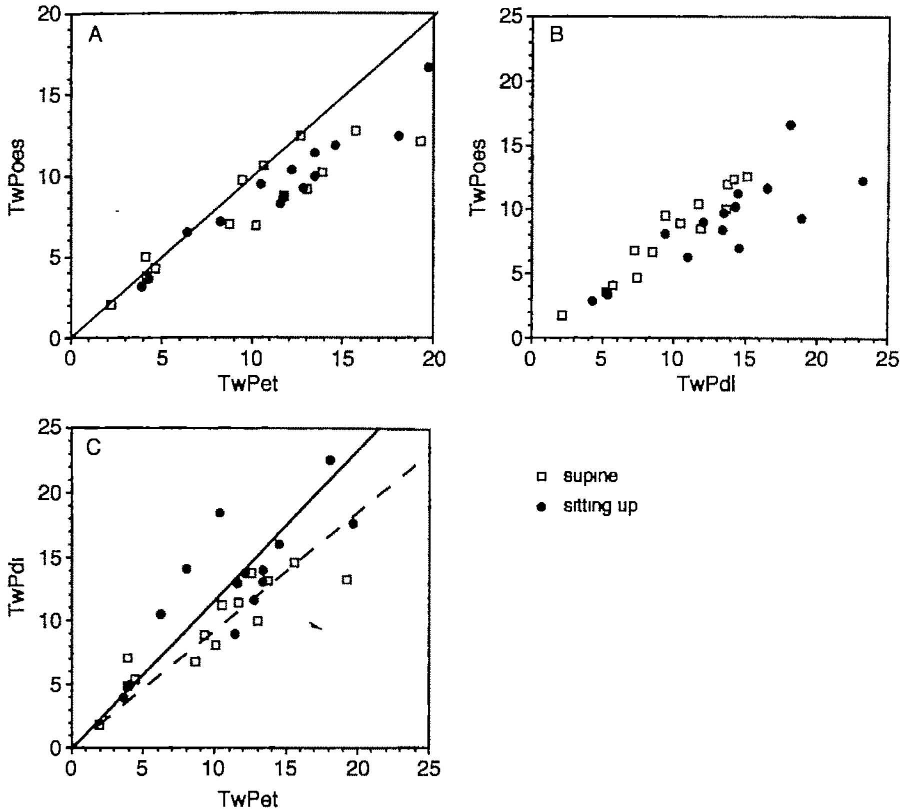

Fig 3 (A) Mean BAMPs TwPoes compared with mean BAMPS TwPet in the supine position and at 45° (cm H_2O) Line of identity is included (B) Mean BAMPS TwPoes compared with mean BAMPS TwPdi in the supine position at 45°. (C) Mean BAMPS TwPdi compared with mean BAMPS TwPet in the supine position and at 45°. Solid regression line indicates TwPet/TwPdi relationship when sitting. Broken regression line indicates TwPet/TwPdi relationship when supine. TwPet generally exceeds TwPoes because TwPoes is adversely affected by local atelectasis and postural effects impeding trasmission of mean pleural pressure. It is likely that the measure TwPoes is an underestimate of mean pleural pressure. Therefore, estimating TwPdi (which has been calculated from the difference between TwPgas and TwPoes) from TwPet values using the regression lines may well tend to produce a slight underestimate of the true TwPdi.

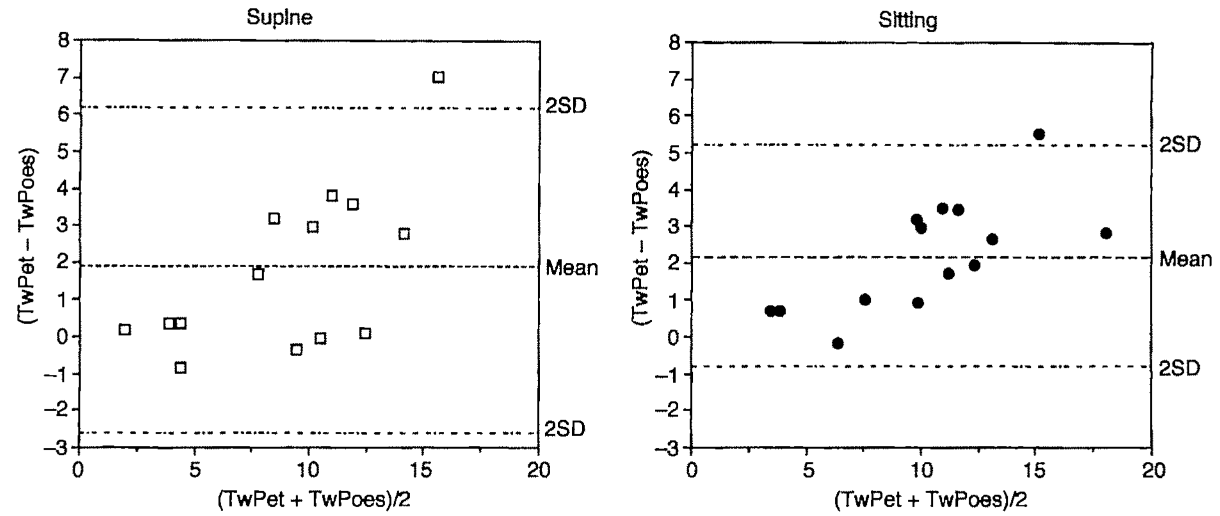

Fig 4 Bland and Altman plots comparing the difference between mean BAMPS TwPoes and mean BAMPS Tw Pet against the average of the two techniques in both positions. The differences between the two techniques vary depending on the size of the twitch pressure change. At high twitch pressures, especially when supine and particularly above 9 cm H_2O, TwPet exceeds TwPoes (2 SD from the mean=2 SD)

Table 1 Pressures are measured in cm of H_2O

	TwPoes supine	TwPet supine	TwPoes/TwPet supine	TwPoes sitting	TwPet sitting	TwPoes/TwPet sitting
	6.9	10.1	0.68	9.9	13.3	0.74
	4.2	4.6	0.92	3.5	4.2	0.83
	1.9	2.1	0.92	8.2	11.4	0.73
	8.7	11.6	0.74	8.5	11.5	0.74
	3.7	4.1	0.92	11.3	13.3	0.86
	6.9	8.6	0.81	16.7	19.5	0.85
	12.1	19.1	0.63	9.4	10.4	0.93
	12.7	15.5	0.82	9.2	12.7	0.73
	10.5	10.5	1.00	7.1	8.1	0.87
	12.4	12.5	0.99	10.3	12	0.88
	9.1	12.9	0.70	11.8	14.4	0.82
	9.6	9.3	1.04	3.1	3.8	0.81
	4.9	4.0	1.26	6.5	6.3	1.04
	10.1	13.7	0.74	12.4	17.9	0.69
Mean	8.1	9.9	0.87	9.1	11.3	0.82
SD	3.5	4.9	0.17	3.5	4.6	0.09

In order to assess the agreement between TwPet and TwPoes we calculated the differences between the means of each of the five stimulations. The mean of these differences is a measure of accuracy or bias whilst the standard deviation (SD) is a measure of precision as presented in Figure 3. Both bias and precision are necessary to assess agreement.[24] We calculated the limits between which 95% of the differences would lie ('limits of agreement', 2 SD).[23] We also calculated the mean and standard deviation of the ratio of mean TwPet: mean TwPoes to enable us to compare the values of the two methods over the range of twitch pressures observed (Table 1).

Bland and Altman plots were constructed to compare the differences between TwPoes and TwPet, against the mean of TwPoes and TwPet (Fig. 3). The ratio of TwPoes to TwPet was calculated to give a measure of the degree of agreement between the two techniques. To assess the spread of data within each set of measurements, the mean coefficient of variation was calculated within each occasion of five twitches in each subject. An average for each occasion for the 14 subjects was then derived.

To assess the spread of data between individuals, the coefficient of variation of TwPoes/TwPet and TwPet/TwPdi were calculated for each position to see if results became more variable in a given posture. TwPgas cannot be measured from mouth or tracheal tube pressures, but if it is a constant fraction of TwPdi in a particular posture, then this would imply that information relating to TwPoes alone may be enough to estimate TwPdi. However, if TwPgas is not a constant fraction of TwPdi, or if this is more of a problem in a particular posture, then estimates of TwPdi will be less reliable. To assess this we calculated the coefficient of variation of mean TwPoes/TwPdi between and within subjects for each posture.

Table 2

		Mean	SD	Coefficient of variation
Suppine	Tw/Poes/TwPet	0.87	0.17	19.7
	TwPoes/Twpdi	0.84	0.11	12.8
	TwPet/TwPdi	1.00	0.22	22.1
Sitting	TwPoes/TwPet	0.82	0.09	11.4
	TwPoes/TwPdi	0.69	0.13	18.9
	TwPet/TwPdi	0.86	0.20	23.3

Table 3

Posture	Equation	r^2	Equation with no intercept	r^2
Supine	TwPoes=0.87×TwPdi–0.3	0.93	TwPoes=0.85×TwPdi	0.99
	TwPoes=0.65×TwPet+1.7	0.84	TwPoes=0.79×TwPet	0.97
	TwPet=1.17×TwPdi–1.3	0.83	TwPet=1.05×TwPdi	0.97
	TwPdi=0.71×TwPet+2.6	0.83	TwPdi=0.92×TwPet	0.97
45°	TwPoes=0.58×TwPdi+1.4	0.66	TwPoes=0.67×TwPdi	0.96
	TwPoes=0.74×TwPet+0.7	0.93	TwPoes=0.80×TwPet	0.99
	TwPet=0.74×TwPdi+1.4	0.65	TwPet=0.84×TwPdi	0.95
	TwPdi=0.87×TwPet+3.5	0.65	TwPdi=1.13×TwPet	0.95

Results

An example of the pressure traces recorded during magnetic stimulation of the phrenic nerves using BAMPS is shown in Figure 2.

Agreement between TwPoes AND TwPet

TwPoes plotted against TwPet for the patients in the supine and sitting up positions are shown in Figure 3. The mean TwPoes was 8.1 cm H_2O and TwPet 9.9 cm H_2O when supine. The mean TwPoes was 9.1 cm H_2O and TwPet 11.3 cm H_2O sitting (Table 1).

The mean difference between TwPoes and TwPet measured in the supine position was –1.8 cm H_2O (SD 2.2) (Fig. 4). As TwPoes and TwPet increased, the difference between the two methods also increased.

The mean difference between TwPoes and TwPet measured in the sitting position was –2.2 cm H_2O (SD 1.5) (Fig. 4). As TwPoes and TwPet increased, the difference between the two pressures also increased.

In order to standardize for the wide range of measured pressures and to better explore these changes, we expressed them as a ratio of TwPoes/TwPet (Table 1).

The 95% confidence intervals for the likely differences (TwPoes – TwPet) between the two techniques over a range of TwPoes from 2 up to 17 cm H_2O in the sitting and supine positions was –5.3 to +1.8 cm H_2O sitting and –6.2 to +2.6 cm H_2O supine. However, the difference between TwPet and TwPoes was less than ±1 cm H_2O at twitch pressures less than 8 cm H_2O when supine and 10 cm H_2O when sitting, and then became greater at higher pressures (Fig. 4).

TwPet was linearly related to TwPoes in both postures. In the sitting position TwPet was related to TwPoes r^2=0.93 and TwPdi r^2=0.65 (P<0.01). In the supine position TwPet was related to TwPoes r^2=0.84 and TwPdi r^2=0.83 (P<0.01). TwPoes was less than TwPet.

Variability

The within occasion coefficient of variation for supine measurements within individual patients was: TwPet 11.6%, TwPoes 14.6%, and TwPdi 11.8%. When sitting the results were similar: TwPet 13.5%, TwPes 13.9%, and TwPdi 11.2%.

The variability of between subject comparisons of TwPoes/TwPet, TwPoes/TwPdi, and TwPet/TwPdi are listed in Table 2 for both the supine and sitting postures. The ratio TwPoes/TwPet was slightly closer to 1.0 in the supine position although the between individual variability of this relationship was greater. On the other hand TwPoes made up a greater fraction of TwPdi supine and TwPoes/TwPdi was more consistent. When TwPet was related to TwPdi variability was relatively high and similar in both positions.

The relationship of TwPet, TwPoes, and TwPdi from linear regression

TwPet, TwPoes, and TwPdi sitting

There were significant linear relationships between TwPet, TwPoes, and TwPdi in both the sitting and supine positions (P<0.01) (Fig. 3 and Table 3).

Mean TwPet in the sitting position was on average 22% greater than TwPoes (P<0.001, Wilcoxan Sign Rank test). The regression equations without intercept describing the relationship between sitting TwPet and sitting up TwPoes produced an almost identical result: TwPet was typically 25% larger than TwPoes (Table 3). Sitting TwPoes made up 67% of TwPdi; and TwPet was equal to 84% of TwPdi.

TwPet, TwPoes and TwPdi supine

In the supine position mean values for TwPet were 26% greater than TwPoes ($P<0.001$, Wilcoxon Sign Rank test). When assessed using linear regression with no intercept, TwPoes made up 85% of TwPdi when supine and TwPet was equal to 105% of TwPdi when supine (Table 3). Therefore, the value for TwPet was a larger fraction of the TwPdi measurement in the supine position compared with the sitting position.

Discussion

We found that TwPet was linearly related to TwPoes in both positions (Figure 3 and Table 3), although the 95% confidence intervals for the likely differences (TwPoes – TwPet) between the two techniques were –5.3 to +1.8 cm H_2O while sitting and –6.2 to +2.6 cm H_2O when supine (Fig. 4). However, the difference between TwPet and TwPoes sitting was less than ±1 cm H_2O at twitch pressures less than 8 cm H_2O when supine and 10 cm H_2O when sitting and greater at higher pressures. The between subjects coefficient of variation for TwPes/TwPdi with BAMPS has previously been found to be between 12%[12] and 15%,[9] which is better than the traditional BES. We therefore anticipated the coefficient of variation for TwPet/TwPdi would be similar. However, the between subjects coefficient of variation of TwPet/TwPdi was above 20% in both positions (Table 2) and so, the precise quantification of diaphragm strength using a regression equation derived from the results of several individuals is not possible with this level of agreement. However, the technique does retain the potential to identify weak patients, who can then be investigated further. In addition the coefficient of variation of TwPoes/TwPdi within an individual over time is 8.7%.[12] This means that it may be possible to follow changes in strength in an individual with repeated non-invasive studies over a period of time.

Factors affecting the transmission of pressure to the oesophagus and airway

TwPet was generally higher than TwPoes. Similar results have been seen in previous studies, when twitch mouth pressures were compared with TwPoes. When positioning the balloon catheters in the ICU after cardiac surgery, we could not achieve perfect 1:1 matching of Poes/Pet during a gentle inspiratory manoeuvre against a closed mouthpiece (mean 0.91 (SD 0.09)). Baydur studied normal subjects in laboratory conditions and could not always achieve a 1:1 relationship, particularly in the supine position, where he achieved an average of 0.96, ranging between 0.86 and 1.1. In practice, our mean of 0.91 could explain why our estimate of Poes compared with airway pressure would differ by 9%. This factor could help explain why TwPet is often slightly larger than TwPoes and probably contributes to the greater coefficient of variation of TwPoes/TwPet when supine (19.7%), compared with 11.4% in the sitting position. Indirect evidence from ^{133}Xe ventilation studies suggested that in supine subjects there might be a gradient of pressure change in the pleura extending from the apex to the base compared to the airway. This may account for some of the difference between Pet and Poes in the supine position.[25 26] Hamnegard found some instances of twitch mouth pressure (TwPmo) exceeding TwPoes in normal subjects.[10] He postulated that the change in TwPmo may more accurately reflect average change in pleural pressure throughout the whole thorax during phrenic stimulation. The same could apply to TwPet measurements.

The difference between TwPet and TwPoes does become more prominent as twitch amplitude increases. This may be a problem of transmission of pressure to the oesophageal balloon, which is more difficult in the supine position.[16] This is also a result of the weight of the heart and mediastinum which compress structures especially the lung, so disturbing the transmission of pressure to the oesophagus. This is even more likely after cardiac surgery when posterobasal atelectasis is extremely common. This makes it difficult to find a position where Poes reflects mean pleural pressure. Therefore, it may be that Poes measured with balloon catheters in these subjects when supine tend to underestimate mean pleural pressure change and TwPet may in fact be a closer estimate.

On the other hand, in patients with abnormal lungs with areas of slow time constants and with intrinsic positive end expiratory pressure (PEEP) it might be expected that TwPet would be less than TwPoes, because of failure of pressure transmission, rather than the opposite.

Cardiac contractions cause 1–2 cm H_2O reductions in the magnitude of Poes in our experience. This feature is more prominent when supine (mean 3.5 (SD 1.8) cm H_2O according to Baydur)[16] and can be seen distorting the TwPoes in Figure 1. This will contribute to the relative reduction in TwPoes compared with TwPet on those occasions when the contraction coincides with the stimulation.

Clearly glottic closure is not a problem in intubated patients, although activation of some of the laryngeal musculature could occur during magnetic stimulation. This might lead to conformational changes in the airway or alter the position of the tracheal tube or its cuff so affecting TwPet. The importance of these factors remains to be quantified.

Some of our TwPdi data in this paper suggest the presence of varying levels of diaphragm weakness (mean TwPdi 11 (SD 4.7) cm H_2O). Our recordings are made after cardiac surgery, which can be associated with phrenic nerve injury or diaphragm weakness. Previous estimates of the incidence of diaphragm dysfunction made slightly later in the postoperative period vary widely.[27–29] Some of our previous data,[21] looks at the first 24 h after cardiac surgery, and does appear to show a higher incidence of diaphragmatic weakness (approximately 50% at 12 h), when compared with Polkey's normal data (normal mean TwPdi 26.8 (SD 5.5) cm H_2O).[30 31] This gradually improved over time. The resulting spread of strength levels is helpful, as it allows us to examine the technique's performance over a range of pressures.

The effect of recent wiring of the sternum on lung mechanics is also difficult to predict. Whether the process of opening and 'spreading' the rib cage affects the intercostal nerves is unknown. The impact on the mechanics of the chest wall could alter chest wall compliance. This in turn would alter the impact that contraction of the diaphragm would have on the ratio of TwPoes/TwPgas, and so alter partitioning. However, this is not evident when our partitioning data is compared with previous work.[9 11] Pain might affect the pressures produced during voluntary efforts, but this is less likely during non-volitional stimulations such as used in this study.

The effect of the contribution of TwPoes and TwPgas to TwPdi

TwPet may be a reflection of the TwPoes component of TwPdi, which forms a larger fraction of TwPdi as we move towards the supine position. Conversely there is a large TwPgas contribution to TwPdi, when sitting, which is not reflected in the TwPoes or TwPet response to diaphragm stimulation. This may explain the lower r^2 value for the association of sitting TwPet with TwPdi and sitting TwPoes with TwPdi. To compound this problem, the fraction of TwPdi made up by TwPoes compared with TwPgas differs greatly between individuals, as seen from the coefficient of variation between individuals of TwPoes/TwPgas: 12.8% supine and 18.9% sitting. Therefore, TwPet may reflect TwPoes, but as TwPoes forms a different fraction of TwPdi in each individual, especially when sitting, and does not reflect the TwPgas component of TwPdi, TwPet while sitting has some limitations in its ability to indicate TwPdi.

We have been able to generate linear equations that allow the prediction of TwPdi from TwPet, but the accuracy of prediction will always be hindered by the lack of a TwPgas measurement and the lack of knowledge of partitioning in that individual. However, as the coefficient of variation of partitioning between occasions within an individual from longitudinal studies is less than 10%, serial measurements of TwPet may still be an effective means of recording changes in diaphragm strength over time for that individual.

In summary, TwPet combined with BAMPS does reflect TwPoes in response to diaphragmatic stimulation, particularly at low strength levels, allowing an estimate of TwPdi from the TwPet measurement, especially when making supine recordings. This may be a useful means of detecting patients with reduced diaphragm contractility who could then be tested further, by more invasive and potentially more precise techniques.

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Difference in sensitivity to vecuronium between patients with ocular and generalized myasthenia gravis

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Patients with myasthenia gravis show sensitivity to non-depolarizing neuromuscular blocking drugs, but little is known about differences in this sensitivity between types of myasthenia. In 10 patients with ocular myasthenia gravis and 10 with generalized myasthenia gravis, twitch tension was monitored in the adductor pollicis muscle by supramaximal train-of-four stimulation of the ulnar nerve during anaesthesia with sevoflurane 2.5% and nitrous oxide 60%. After baseline measurement, an initial dose of vecuronium 10 $\mu g\ kg^{-1}$ was given. When the twitch height stabilized (maximum block after the first 10 $\mu g\ kg^{-1}$), the next incremental dose of 10 $\mu g\ kg^{-1}$ was given and repeated until block, defined as [1–(first twitch/baseline first twitch)]×100 reached 90%. Maximum block after the first dose of vecuronium in ocular patients was significantly less than that in generalized patients (median 51 *vs* 91%; $P<0.05$). Onset of block after the first dose of vecuronium was significantly slower in ocular than in generalized myasthenic patients (mean 300 *vs* 200 s; $P<0.05$). Doses required to attain a block of 90% or more were significantly higher in ocular than in generalized patients (median 20 *vs* 10 $\mu g\ kg^{-1}$; $P<0.05$). Clinicians should consider the type of disease according to the Osserman classification when using non-depolarizing neuromuscular blocking drugs in patients with myasthenia gravis.

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Myasthenia gravis is an autoimmune disorder characterized by muscular fatigue that worsens with exertion. Patients with myasthenia gravis require special care during anaesthesia because of their sensitivity to non-depolarizing neuromuscular blocking drugs,[1–5] resulting from a reduced number of functioning acetylcholine receptors (AChR) at the neuromuscular junction.[6] A wide range of effective doses of vecuronium have been shown to be required to obtain 95% neuromuscular block (ED_{95}) in myasthenic patients, varying from 6 to 44 $\mu g\ kg^{-1}$.[2 3] The wide variation in the severity of myasthenia, which is categorized using the Osserman classification,[7] may be one explanation for the varied sensitivity to vecuronium, but little has been reported about this possibility. Hypothesizing that ocular myasthenic patients would be less sensitive to vecuronium than generalized myasthenic patients, we compared neuromuscular responses to vecuronium in the adductor pollicis muscle between these groups.

Methods

After we had received approval of the study protocol from the Institutional Ethics Committee of our hospital and obtained individual patients' informed consent, we studied 20 myasthenic patients (10 with ocular disease and 10 with generalized disease, representing types I and II in the Osserman classification[7] respectively) who were scheduled to undergo thymectomy. The diagnosis was confirmed by the presence of circulating antibody to the AChR and a positive response to edrophonium in addition to typical

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clinical and laboratory findings (ptosis, diplopia, limb weakness, and a decremental conduction response on electrical stimulation of the nerve supply to the orbicularis oculi or the deltoid muscle). The generalized patients showed limb weakness or a decremental response in the deltoid muscle to repetitive motor nerve stimulation.

Binding and blocking antibodies to AChR were measured preoperatively in serum samples. To determine binding antibody, α-bungarotoxin labelled with ^{125}I was bound to prepared antigenic human AChR (^{125}I-AChR). Sera from patients were incubated with ^{125}I-AChR. Antigen–antibody complexes were precipitated by incubation with anti-human IgG. Radioactivity in the precipitate was measured with a gamma counter.[8] When measuring binding antibody, it is impossible to detect the antibody in the area near the acetylcholine binding site of the receptor. Thus, blocking antibody to the acetylcholine binding site was also measured. Sera from patients and controls were incubated with prepared antigenic AChR followed by incubation with ^{125}I-labelled α-bungarotoxin. Aliquots were then applied to Sepharose columns to measure the percentage inhibition of labelled toxin binding with AChR.[9]

Anticholinesterase medication was continued until the morning of surgery. The patients were premedicated with hydroxyzine 50 mg and atropine 0.5 mg, given 1 h before induction of anaesthesia. Anaesthesia was induced with thiopental 4 mg kg^{-1} and fentanyl 2 μg kg^{-1} followed by inhalation of sevoflurane 2.5% and nitrous oxide 60% in oxygen. The lungs were ventilated by face-mask so that the end-tidal carbon dioxide pressure was maintained at about 5.3 kPa. Skin temperature over the thenar region was monitored and was maintained at 32–33°C. Non-invasive blood pressure was measured every 5 min, and when systolic blood pressure had decreased to <80 mm Hg ephedrine 5 mg was administered i.v.

Neuromuscular transmission was monitored by measuring twitch tension in the adductor pollicis muscle (Myograph 2000; Biometer International, Odense, Denmark). The ulnar nerve was stimulated at the wrist using surface electrodes with supramaximal train-of-four (TOF) square-wave pulses of duration 0.2 ms every 12 s (Myotest, Biometer International). When the twitch response had remained stable for at least 10 min, the baseline height of the first twitch (T1) was measured. The TOF ratio, expressed as a percentage, was defined as the ratio of the fourth to the first response to TOF stimulation. After baseline measurements, an initial dose of vecuronium 10 μg kg^{-1} was administered i.v. Maximum block was defined as the maximum effect of the first dose of vecuronium 10 μg kg^{-1}. The next incremental dose of vecuronium 10 μg kg^{-1} was given after the twitch had again stabilized. As long as neuromuscular block, defined as [1–(T1/baseline T1)]×100, was less than 90%, additional doses of vecuronium were given until 90% or greater block had been achieved. The trachea was then intubated and the inspired concentration of sevoflurane was decreased from 2.5% to between 0.5 and 1.5%. Responses in the adductor pollicis muscle were monitored continuously. Maximum block produced by vecuronium 10 μg kg^{-1} and the time to the onset of maximum block were recorded.

Statistics

Parametric data are presented as mean (SD) and non-parametric data as median (range). Parametric data were analysed with the *t* test and non-parametric data with the Mann–Whitney *U* test. A *P* value less than 0.05 was considered to indicate significance.

Results

No significant differences were found between the ocular and generalized groups with respect to age, sex, weight, duration of disease or serum concentration of binding antibody to AChR. Blocking antibody was significantly higher in the generalized group than in the ocular group. The generalized group included five type IIa (mild, generalized) and five type IIb (moderate, generalized) patients according to the Osserman classification. Two patients in the ocular group and six patients in the generalized group received pyridostigmine (Table 1). Before vecuronium was administered, median TOF ratios were 95% (range 85–98%) in the ocular group and 91% (55–100%) in the generalized group. No significant difference in TOF ratios was evident between groups. After vecuronium 10 μg kg^{-1}, the ocular group showed a lower maximum block [median (range) 51 (0–98)% *vs* 91 (40–100)%], a slower onset of block [mean (SD) 300 (73) *vs* 200 (74) s] and greater total doses needed to exceed 90% block [median (range) 20 (10–30) *vs* 10 μg kg^{-1} (10–20 μg kg^{-1})] than the generalized group (P<0.05). Two patients in the ocular group had at least 90% block, as did six patients in the generalized group. No patient showed 100% block in the ocular group, while three patients did in the generalized group. Mean onset of maximum neuromuscular block took over 200 s in all patients in the ocular group, whereas six patients in the generalized group took less than 200 s. In the ocular group, three patients required vecuronium 30 μg kg^{-1} to exceed 90% block. In contrast, in the generalized group no patient required 30 μg kg^{-1} (Table 2).

Discussion

Although one might expect to see a difference in sensitivity to neuromuscular blocking drugs between patients with different types of myasthenia gravis, such differences have not been established.[10 11] In this study of 20 myasthenic patients, the 10 patients in the ocular group showed significantly less neuromuscular block after vecuronium 10 μg kg^{-1} than the 10 in the generalized group. The ocular group also showed a more gradual onset of block. The median dose required to produce at least 90% block in the

Table 1 Patient characteristics Summary values are mean (SD) or median (range) *Binding antibody to AChR (normally <0.37 pmol l^{-1}); †blocking antibody to AChR (normally <10%), ‡$P<0.05$ *vs* generalized group

Patient	Age (yr), sex	Weight (kg)	Osserman classification	Duration of disease (months)	Binding antibody* (pmol ml^{-1})	Blocking antibody† (%)	Pyridostigmine therapy (mg day^{-1})
Ocular group							
1	50, M	49	I	5.5	0.67	21	–
2	40, F	70	I	2.5	1.6	12	–
3	72, F	45	I	84	0.9	1.4	–
4	73, F	52	I	1.5	24	12	120
5	40, F	43	I	6	35	9.5	–
6	62, F	59	I	5	0.6	0	180
7	63, M	69	I	5	2.1	7.5	–
8	68, M	66	I	24	3.5	11	–
9	70, F	56	I	15	5.1	10	–
10	72, F	48	I	6	17	15	–
	61 (13)	56 (10)		15 (25)	9 (12)	10 (0–12)‡	
Generalized group							
1	43, M	58	IIa	40	0.93	40	–
2	58, M	55	IIa	34	6.0	41	180
3	69, F	50	IIa	80	63	10	90
4	52, F	48	IIa	12	48	29	120
5	57, F	57	IIa	3	35	3.2	–
6	37, M	62	IIb	2.5	2.4	19	180
7	23, F	54	IIb	15	6.5	39	–
8	53, F	64	IIb	11	2.0	39	240
9	48, F	47	IIb	90	13	29	–
10	53, F	49	IIb	7	0.9	10	90
	49 (13)	54 (6)		29 (32)	17 (23)	29 (10–41)	

ocular group was twice that required in the generalized group. Thus, ocular myasthenic patients were less sensitive to vecuronium than the patients with generalized myasthenia.

As sensitivity to non-depolarizing neuromuscular blocking drugs is increased in myasthenic patients,[1–6] we used an initial dose of vecuronium 10 μg kg^{-1}, which is smaller than the priming dose used ordinarily.[12 13] Sensitivity to non-depolarizing neuromuscular blocking drugs is known to vary greatly between myasthenic patients. Several studies using a cumulative technique have shown the ED_{95} for vecuronium to range from 6 to 44 μg kg^{-1}.[2 3] Although one patient in our ocular group showed 98% block with vecuronium 10 μg kg^{-1}, exceeding the median value for maximal block in the generalized group, the ocular myasthenic patients as a whole showed less sensitivity to vecuronium than the generalized myasthenic patients.

In myasthenia gravis, the ocular muscles are affected most commonly, being involved initially in 40% of cases. It is rare for the initial symptoms to be limited to limb muscles.[6] However, intraoperative neuromuscular monitoring is commonly performed in the upper limb. Our data show that the limb muscles of ocular myasthenic patients are significantly less sensitive to vecuronium than those of generalized myasthenic patients. Differences in sensitivity between ocular and generalized myasthenia gravis patients probably occur because the disease induces different degrees of change in the margin of safety for neuromuscular transmission in the limb muscles. In ocular patients,

Table 2 Mechanomyographic data and total vecuronium dose required to achieve at least 90% block in each of the patients studied Summary values are median (range) or mean (SD) Maximum block (%) = maximum depression of [1–(T1/baseline T1)]×100 after vecuronium 10 μg kg^{-1}, where T1 is the first TOF response. *Interval between injection of vecuronium and maximum block, †type I in the Osserman classification, ‡type II in the Osserman classification, §$P<0.05$ *vs* generalized group

Patient	Baseline TOF ratio	Maximum block (%)	Onset of block (s)*	Total dose (μg kg^{-1})
Ocular group†				
1	98	31	276	30
2	94	87	264	20
3	97	0	262	30
4	97	90	264	10
5	85	98	300	10
6	96	46	348	20
7	98	38	264	30
8	98	63	216	20
9	93	55	288	20
10	95	37	480	20
	95 (85–98)	51 (0–98)§	300 (73)§	20 (10–30)§
Generalized group‡				
1	100	40	288	20
2	95	47	192	20
3	92	100	149	10
4	94	71	229	20
5	87	100	168	10
6	80	100	168	10
7	55	98	60	10
8	77	90	252	10
9	90	92	168	10
10	100	79	312	20
	91 (55–100)	91 (40–100)	200 (74)	10 (10–20)

clinically important decreases in this margin of safety occur only in ocular muscles. In contrast, generalized myasthenic patients show a decreased margin of safety in all skeletal muscles, including the adductor pollicis.

The ED_{50} for vecuronium has ranged from 0.3 to 19 μg kg^{-1} and the ED_{90} from 5 to 35 μg kg^{-1} in myasthenic patients.[1–3] In these studies, most patients represented type II in the Osserman classification, like the patients with generalized myasthenia in our study. Additionally, type IV patients (with late, severe generalized myasthenia) were included in the study of Eisenkraft and colleagues.[2] Only one patient of this type was studied by Buzello and colleagues.[1] Patients in our generalized group were similar in disease severity to most subjects in previous studies. However, patients in our ocular group had milder myasthenia than the individuals studied previously. Although we did not calculate effective doses of vecuronium, our data showed a difference in sensitivity between ocular and generalized patients.

Our data were obtained under nitrous oxide–sevoflurane anaesthesia; in previous reports of myasthenic patients, neuromuscular variables were measured in the absence of potent anaesthetic agents. Generally, inhaled anaesthetics decrease the availability of acetylcholine at the neuromuscular junction[14] and increase the neuromuscular block produced by non-depolarizing neuromuscular blocking drugs,[15–17] but this effect has not been specifically confirmed in myasthenic patients. Vanlinthout and colleagues[15] reported ED_{50} and ED_{95} values for vecuronium in neurologically healthy patients during anaesthesia with sevoflurane 1.7% of 14.4 and 34.9 μg kg^{-1} respectively, which are 42 and 32% less than when inhaled anaesthetics are not used. The generalized myasthenic patients in this study, who were apparently similar to the myasthenic patients in previous studies of vecuronium, showed 91% block from vecuronium 10 μg kg^{-1}. Although comparisons between studies have limitations, the block produced appeared to be greater in our study than in previous studies of myasthenia gravis; the sensitivity to vecuronium was probably increased by sevoflurane in myasthenic patients as well as in our patients with normal neuromuscular transmission.

However, the use of inhalational anaesthetics does not affect the results of this study, which compared the sensitivity to vecuronium of two types of myasthenia. One limitation of this study, however, may be that we did continue the morning dose of anticholinesterase. The incidence of TOF fade before administration of vecuronium, which is well tolerated in myasthenia gravis patients, was low in our patients; this may have been caused by the administration of pyridostigmine. The other limitation was the interval between TOF stimuli. It has not been established in patients with myasthenia gravis that an interval as long as 12 s between TOF stimuli is sufficient. The twitches may thus have been affected by preceding stimuli. We standardized the interval at 12 s, as used in neurologically healthy patients, as any effect of myasthenia in this respect has not been shown.

In summary, we estimated neuromuscular block produced by vecuronium in the adductor pollicis muscle in patients with ocular and generalized myasthenia. Ocular myasthenic patients were less sensitive to vecuronium than generalized myasthenic patients. During general anaesthesia, neuromuscular monitoring is essential to avoid problems of prolonged neuromuscular block in myasthenic patients; however, the degree of block produced by a given dose of vecuronium is likely to be less in ocular than in generalized myasthenic patients.

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Platelet function during pregnancy: an evaluation using the PFA-100 analyser

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In clinical practice, the only tests of platelet function are bleeding time and platelet number. Bleeding time lacks sensitivity and specificity but the PFA-100, an *in vitro* analyser of platelet function may be of value. This study aimed to evaluate any correlation between platelet number and function using the PFA-100 in pregnant women. During a 21-month period, platelet function was evaluated in whole blood as part of the pre-anaesthetic coagulation testing screen with the PFA-100 using collagen and epinephrine (PFA-EPI) or ADP (PFA-ADP) as platelet agonists. Thrombocytopenia was defined as a platelet number less than150 G litre^{-1}. The patients were divided into four groups: Group I (n=110) normal pregnancy; Group II (n=38) thrombocytopenia of pregnancy; Group III (n=13) women with pre-eclampsia without thrombocytopenia; Group IV (n=19) women with pre-eclampsia and thrombocytopenia. Results are expressed as mean (SD). Platelet count was not statistically different between Groups II and IV (111.1 (23.1) *vs* 99.5 (28.0) G litre^{-1}). PFA-EPI was statistically increased in Group II (124.0 (26.3) s), Group III (128.3 (17.9) s), and Group IV (143.6 (47. 7) s) compared with normal pregnant patients (114.6 (27.3) s, $P<0.05$, Mann–Whitney *U*-test). PFA-ADP was statistically increased only in Group II compared with normal pregnant patients (90.5 (18.9) *vs* 80.2 (11.2) s, $P<0.05$). PFA values were increased above normal laboratory values in (four of 38) Group II patients and (six of 19) Group IV patients but in no patients in Group III. PFA-ADP results were correlated with platelet count only in Group IV (r=–0.74, P=0.0003). The increased PFA values and the correlation between PFA-ADP and platelet number in hypertensive thrombocytopenic women confirms that platelet function may be decreased in such patients. In patients with pregnancy-induced thrombocytopenia, platelet function may be preserved when the platelet count is as low as 60 G litre^{-1}.

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Until recently, only two tests could be performed to evaluate platelet function in a routine clinical setting. Bleeding time, which is highly operator-dependent, lacks sensitivity and specificity and has a poor diagnostic value even when platelet function is altered.[1 2] Platelet aggregation tests cannot be used in usual practice and like the bleeding time, cannot predict the risk of haemorrhage. However, during pregnancy, knowledge of platelet function may be of critical importance before performing epidural anaesthesia. Indeed, platelet count may be decreased at the end of the third term of normal pregnancy in about 0.3% of women despite an increased platelet aggregability.[3] In contrast, 28% of women with pre-eclampsia may have platelet counts of less than 150 G litre^{-1}.[4] Thrombocytopenia less than 100 G litre^{-1} is only observed in severe pre-eclampsia.[4] In such patients, regional anaesthesia has been performed without any subsequent neurological complications,[5–8] even when decreased platelet function has been documented from both platelet aggregation tests and bleeding times.[9 10] In pre-eclampsia patients, the platelet count above which epidural anaesthesia may be performed safely is not known. This may explain why there is still controversy regarding the value of measuring the platelet count at the end of pregnancy. The recent report of a spinal haematoma following epidural anaesthesia in an eclamptic woman with thrombocytopenia reinforces the need for a reprodu-

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Table 1 Physical characteristics of patients Mean (SD), $^*P<0.05$ compared with Group I, $^\dagger P<0.05$ compared with Group II Group I, normal patients; Group II, pregnancy-induced thrombocytopenia; Group III, PIH women without thrombocytopenia, and Group IV, PIH women with thrombocytopenia

	Group I (*n*=110)	**Group II** (*n*=38)	**Group III** (*n*=13)	**Group IV** (*n*=19)
Age (yr)	28.7 (16–41)	28.9 (19–41)	27.9 (19–38)	28.6 (21–37)
Age of pregnancy at sampling time (weeks)	38.2 (1.3)	38.4 (2.0)	36.0 (3.3)*†	34.1 (4.5)*†
Time from sampling to delivery (days)	11.9 (8.3)	11.6 (10.3)	13.7 (12.6)	6.0 (9.1)*†
Regional anaesthesia	66/110	21/38	10/13	8/19
Caesarean section	18/110	7/38	7/13	15/19

Table 2 Laboratory data at the time of sampling Mean (SD), $^*P<0.05$ *vs* Group I, $^\dagger P<0.05$ *vs* Group II Group I, normal patients, Group II, pregnancy-induced thrombocytopenia; Group III, PIH women without thrombocytopenia, and Group IV, PIH women with thrombocytopenia

	Group I (*n*=110)	**Group II** (*n*=38)	**Group III** (*n*=13)	**Group IV** (*n*=19)
Platelet count (G litre^{-1})	218.9 (51.3)	111.1 (23.1)*	281.4 (63.8)*†	99.5 (28.0)*
Haematocrit (%)	35.9 (3.0)	36.4 (3.3)	35.8 (2.5)	37.2 (3.6)
PFA–Epi (s)	114.6 (27.3)	124.0 (26.3)*	128.3 (17.9)*	143.6 (47.7)*
PFA-ADP (s)	80.2 (11.2)	90.5 (18.9)*	85.0 (11.2)	89.3 (26.5)
APTT ratio	0.94 (0.08)	0.97 (0.07)	0.95 (0.07)	1.11 (0.25)*
PT INR (%)	95.8 (11.1)	99.2 (13.6)	95.1 (8.1)	104.7 (11.9)*
Fibrinogen (g litre^{-1})	4.8 (0.8)	4.6 (0.5)*	5.2 (1.0)†	5.1 (1.1)†

cible and accurate test to evaluate platelet function in this clinical setting.[11]

The PFA-100 platelet function analyser may be of value in such circumstances. The PFA-100 evaluates *in vitro* primary haemostasis by measuring the time required for whole blood to occlude an aperture in the membrane of a test cartridge, which is coated with platelet agonists. A sample (500 μl) of citrated blood is placed in the reservoir of the test cartridge, which is maintained at 37°C. It is aspirated under steady vacuum into the stainless steel capillaries, through which there is a central aperture cut into the membrane covered with collagen and the platelet agonist, epinephrine (PFA-EPI), or adenosine diphosphate (PFA-ADP). Platelet activation and aggregation occurs on the membrane leading to occlusion of the aperture and the interruption of blood flow.[12] This test is easy to perform and gives reproducible results, measured in seconds and similar to *in vitro* aggregation tests, within a few minutes.[13] Moreover, as this test is performed on whole blood, it can evaluate platelet function in its natural environment. This study in pregnant patients aimed to determine if there is a correlation between platelet count and platelet function as assessed by the PFA-100 analyser.

Methods

After local ethical committee approval and informed consent, platelet function was assessed at the end of pregnancy during the anaesthetic visit on the first 110 normal pregnant patients studied and each time a patient presented with thrombocytopenia or pregnancy-induced hypertension (PIH) over a 21-month period. Platelet count, activated partial thromboplastin times (APTT), prothrombin times (PT) and fibrinogen levels were also performed. PFA-100s (Dade Behring, Mannheim, Germany) were carried out by one of the authors with 2 ml of whole citrated blood within 1 h of sampling. Two types of cartridge containing porous membranes covered with collagen and either ADP (PFA-ADP) or epinephrine (PFA-EPI) were used. According to the recommendations of the manufacturer, the PFA-100 results were considered abnormal when the occlusion time was higher than 160 s for PFA-EPI and 120 s for PFA-ADP. Patients were defined as normal (Group I) when they had no thrombocytopenia, hypertension, or past history of clinical bleeding, and clinical examination revealed no bleeding tendency. The other patients were divided into three groups according to the presence of thrombocytopenia (platelet count <150 G litre^{-1}) and/or PIH: Group II, normal pregnancy with thrombocytopenia; Group III, hypertension of pregnancy without thrombocytopenia; and Group IV, hypertension with thrombocytopenia.

Results are reported as mean (SD) and compared between groups using two tailed *t*-tests or Mann–Whitney *U* tests according to the homogeneity of variance (Bartlett tests). Barnet Woolf and Fisher exact tests were used for non-parametric data. Correlations between biological tests were performed in each group by regression analysis. A $P<0.05$ was considered significant.

Results

The physical characteristics of the patients are presented in Table 1. None of the patients were in labour at the time of sampling. The laboratory data of the patients are shown in Table 2. In Group II (38 women), the platelet count was less than 100 G litre^{-1} in 14 samples, and between 100 and 125 G litre^{-1} in 13 samples. In the 19 patients in Group IV, platelet count was less than 100 G litre^{-1} in 11 samples, less than 125 G litre^{-1} in four patients, and less than 150 G litre^{-1} in four patients. This distribution was not statistically different

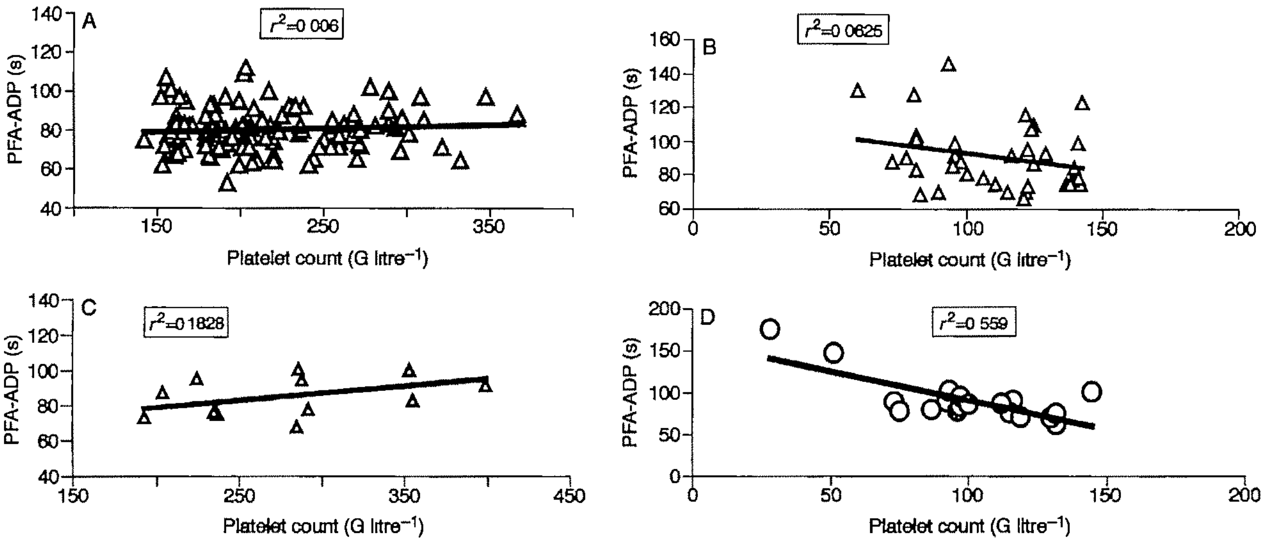

Fig 1 PFA-100 results obtained with collagen and ADP agonists compared with the corresponding platelet count in Group I, normal patients (A); Group II, pregnancy-induced thrombocytopenia (B), Group III, hypertensive women without thrombocytopenia (C); and Group IV, hypertensive women with thrombocytopenia (D). A significant correlation was only found in Group IV.

between Groups II and IV using Barnet Woolf tests (P>0.05).

PFA-EPI was statistically increased in Groups II, III, and IV compared with Group I (Table 2) whereas PFA-ADP was only increased in Group II compared with Group I (Table 2). When looking at individual results, PFA-ADP levels were within normal limits in all the patients from Groups I and III but higher in four patients from Group II and two from Group IV (P<0.01 by Barnet Woolf test). PFA-EPI was slightly increased above normal values in six samples from Group I, three samples from Group II, four from Group IV, and none from Group III (P>0.05 between groups by Barnet Woolf test; P=0.04 between Groups 1 and II or IV by Fischer exact test). Four out of 38 samples in Group II, and six of 19 in Group IV had platelet function abnormality as measured by PFA-100 whereas none in Group III had platelet function abnormality (P<0.01 by Barnet Woolf test). No correlation was observed between platelet count and PFA-EPI or PFA-ADP in any group except in Group IV where PFA-ADP was correlated with platelet count (P=0.0003, r=–0.74) (Fig. 1A–D). When patients with the lowest platelet values were excluded, this correlation disappeared. PFA values were not correlated with haemoglobin except in Group II for PFA-EPI (P=0.011, r=–0.41). No other correlation was observed between PFA results and coagulation data.

Discussion

PFA-100, a global test of platelet function, is capable of diagnosing von Willebrand disease and various congenital platelet defects such as Bernard–Soulier syndrome or Glanzmann's thrombasthenia with higher sensitivity and specificity than the bleeding time.[13] It is, however, similar in its sensitivity and specificity to platelet aggregation tests.[13] PFA-100 is a whole blood test able to measure the ability of platelets to occlude a vascular breach whereas a platelet aggregation test evaluates only platelet function in plasma. In this study, all the PFA-ADP values were normal in otherwise healthy patients whereas PFA-EPI was increased in six patients. This suggests that PFA-EPI may either give false positive values, probably a result of technical problems, or may not be clinically relevant in this setting. However, we cannot exclude oral intake of drugs or food interfering with platelet function without inducing clinical bleeding in these patients. Moreover, such a discrepancy between PFA-ADP and PFA-EPI has already been shown in patients given aspirin suggesting that PFA-EPI may be more sensitive or less relevant than PFA-ADP.[14 15] As we did not carry out platelet aggregation tests in this study, however, we cannot recommend performing only PFA-ADP without performing PFA-EPI simultaneously.

In women with pregnancy-induced thrombocytopenia, mean values of PFA were increased compared with normal pregnant patients suggesting that despite a pregnancy-induced increased platelet reactivity, platelet function is lowered. However, despite platelet values lower than 100 G litre^{-1} in approximately half of the patients, only four had PFA values slightly increased above normal, with PFA-ADP and PFA-EPI both increased in three of them. This demonstrates that overall platelet function remains within physiological values in most of the patients with pregnancy-induced thrombocytopenia despite a platelet count below 100 G litre^{-1}. In normal pregnant women, platelet reactivity is known to be increased, if platelet agonists such as ADP are still present, counterbalancing the decreased platelet number.[3] Despite such reassuring results, it must be noted that in only one patient from Group II was the platelet count lower than 70 G litre^{-1} (namely 60 G litre^{-1}) and thus these results cannot be extrapolated to normal pregnant patients with even lower platelet counts. As no platelet aggregation test was performed in our patients, we cannot explain the increased PFA values in women with a low platelet count but without pre-eclampsia. It is striking, however, that in pregnancy-induced thrombocytopenia, the PFA results were not correlated with platelet count but with the haemoglobin level, suggesting that overall platelet function in whole blood was preserved despite the low platelet number, unless anaemia was present. Erythrocytes act as physiological ADP donors in whole blood and it has already been observed that anaemia may influence PFA results.[16] The correlations between PFA-EPI and haemoglobin levels suggest that, in patients with pregnancy-induced thrombocytopenia, whole blood platelet function depends on erythrocytes, and that one must be especially cautious about an increased bleeding risk when low platelet and erythrocyte counts coexist. These results may also explain the increased bleeding risk associated with thrombocytopenia in the presence of anaemia.[17]

In patients with pre-eclampsia-induced thrombocytopenia, the increase in PFA-EPI and the correlation observed between platelet number and PFA-ADP values demonstrates that a decrease in platelets interferes with platelet function. The absence of a statistical increase in PFA-ADP values in this group may result from a lower sensitivity of this test and/or an insufficient number of patients, particularly if the platelet count is lower than 50 G litre^{-1}. In pre-eclamptic patients, lower platelet reactivity related to depletion of granules stored in the platelets has been demonstrated by decreased platelet aggregation and increased bleeding time.[3 10] Because of its low sensitivity and specificity, the bleeding time has been criticized and other tests, such as the Thrombelastograph® (TEG®), have been proposed to evaluate platelet function in whole blood. In pre-eclamptic patients, it has been shown from whole blood thrombelastography, that a correlation exists between platelet count and reduced platelet function especially in severe cases.[18] Neither TEG® nor platelet aggregation tests were studied in our patients. However, the correlation between platelet number and function assessed by PFA-100 paralleled the results obtained by others with TEG® or bleeding time.[10 18 19] The higher reliability and ease of use of the PFA-100, especially with ADP as the agonist, suggests that this test might be an alternative method of evaluating platelet function in pre-eclamptic patients with low platelet counts. This remains to be demonstrated.

This is the first study reporting platelet function assessed by the PFA-100 in pregnant women. PFA-100 is not correlated with platelet count in women exhibiting pregnancy-induced thrombocytopenia suggesting that platelet function is well preserved in most of these patients at least when the platelet count is over 70 G litre^{-1}, unless anaemia is present. In women with pre-eclampsia, PFA-100 values remained near normal until the platelet count decreases to around 50 G litre^{-1}. The clinical value of PFA-100 in such patients remains to be demonstrated.

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BJA

LABORATORY INVESTIGATIONS

Diffusion of nitrous oxide into the pleural cavity[†]

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We postulated that nitrous oxide transfer into the pleural cavity can occur by diffusion from the alveoli, independent of vascular transport. Under general anaesthesia, six sheep were studied in two phases, a control and an experimental phase. The sheep were anaesthetized, intubated, and received positive pressure mechanical ventilation. A catheter was placed in the right pleural cavity and 150 ml air injected. The animals were ventilated with 100% oxygen. The inspired gas was changed to a mixture of 50% nitrous oxide and 50% oxygen, and the rate of increase of nitrous oxide concentration in the pleural space was measured. The animals were then ventilated with 100% oxygen and then killed by exsanguination while ventilation was continued. The inspired mixture was changed to 50% nitrous oxide and 50% oxygen and the rate of increase in nitrous oxide concentration was measured in the pleural space again. During venitlation with nitrous oxide in the living animals, the concentration of nitrous oxide in the pleural cavity increased rapidly and decreased to zero during ventilation with 100% oxygen. During ventilation without circulation, the rate of increase in the concentration of nitrous oxide in the pleural cavity was the same as in the control phase. This suggests that nitrous oxide enters the pleural space by diffusion, rather than by vascular delivery. This mechanism may explain the rapid increase in the volume of pneumothorax if nitrous oxide is given in the inspired gas.

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Previous studies suggest that vascular transport of inhaled nitrous oxide causes the rapid increase in size of a preexisting pneumothorax.[1 2] Eger and his colleagues studied the time course of volume and concentration changes in two gas-filled cavities: the intestine and the pleural spaces of dogs. When nitrous oxide was administered, a substantial difference was noted in the doubling time of the volume of gas in an artificially created pneumothorax (10 min) compared with an intestinal loop (2 h).[2] Associated with the increase in volume, they noted an initial rapid increase in nitrous oxide concentration in the intrapleural space, followed by a slower progressive change. The difference in the rate of increase in nitrous oxide concentration in the bowel compared with the pleural space was thought to be because of a greater blood flow to the pleura. The difference in the blood gas partition coefficient of nitrous oxide (0.46) and nitrogen (0.014) resulted in the preferential transfer of nitrous oxide into a compliant air filled cavity faster than nitrogen could exit.[2] This is considered responsible for the rapid increase in size of a pneumothorax when a patient inspires a mixture of oxygen and nitrous oxide.

We questioned the ability of blood to deliver the relatively large volumes of nitrous oxide needed to rapidly affect its concentration in a large cavity. We postulated that the delivery of nitrous oxide to the pleural cavity is by direct diffusion from the alveoli rather than by vascular delivery.

Methods

Six sheep were studied in two phases, a control phase followed by an experimental phase. The study design was reviewed and approved by our institutional Animal Studies

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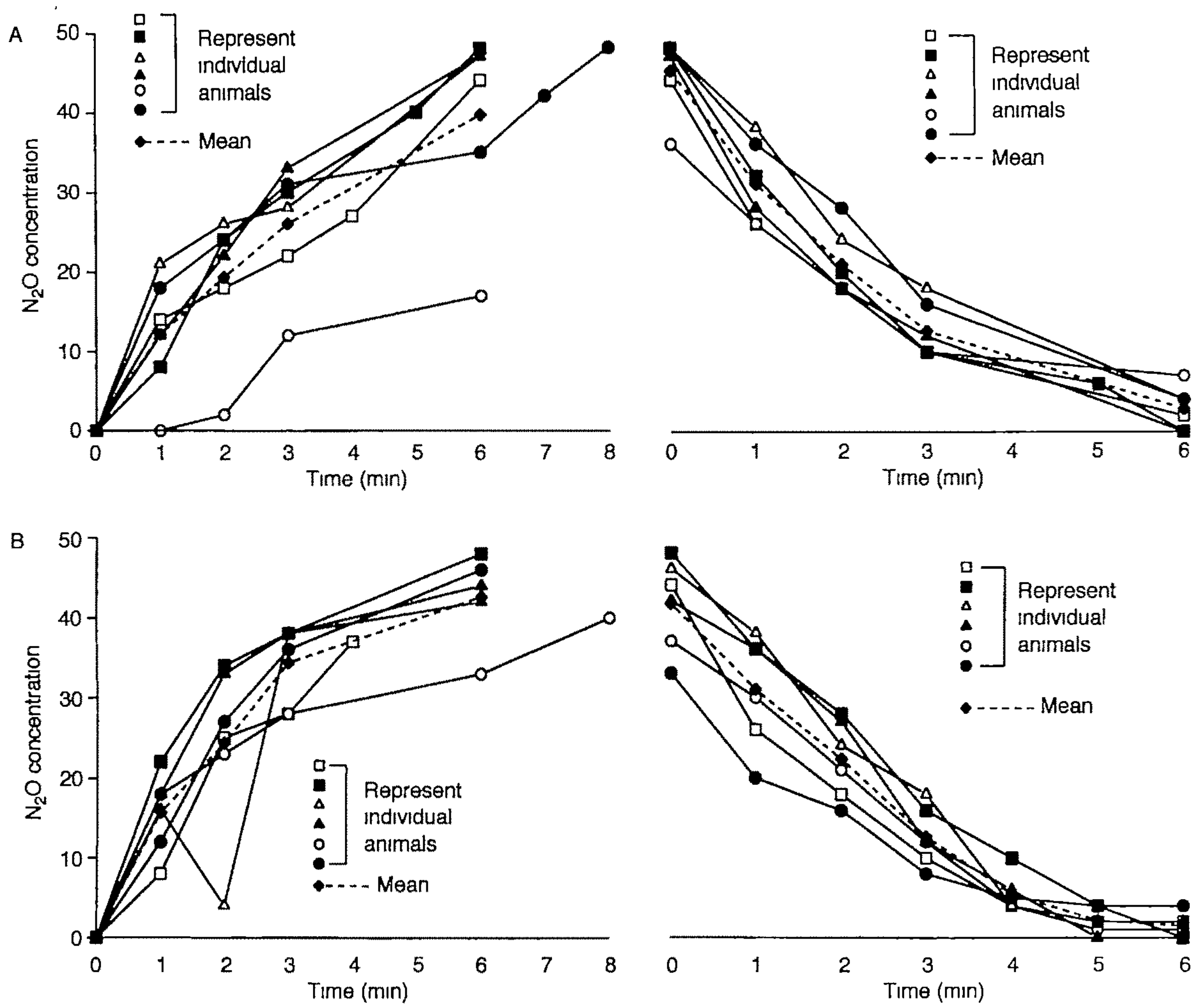

Fig 1 Change in nitrous oxide concentration with time in the control phase (A) and the experimental phase (ventilation without circulation, B) during administration of 50% nitrous oxide (left side of panel), followed by administration of 100% oxygen (right side of panel)

Review Committee in accordance with American Physiological Society/National Institute of Health guidelines. Anaesthesia was induced with an i.m. injection of ketamine (1 mg kg^{-1}), and i.v. access secured. Glycopyrrolate (0.2 mg i.v.) was given to decrease secretions. After administration of pancuronium 1 mg kg^{-1} i.v., the animal was intubated with a size 8.0 cuffed tracheal tube and controlled ventilation was started (Ohmeda 7000 ventilator) using a semiclosed circle system. A 14-gauge catheter was placed in the right femoral artery to measure arterial pressure and allow arterial blood gas sampling. Anaesthesia was maintained with isoflurane (1% inspired) and muscle relaxation maintained (pancuronium 2 mg i.v. every 30–45 min). A gas analyser (Ohmeda RGM 5250) was used to analyse inspired and expired oxygen, carbon dioxide, and nitrous oxide concentrations. Baseline arterial blood gas analysis was performed (Instrumentation Laboratories 16/40 pH, Blood Gas, Electrolytes Analyzer, Lexington, MA, USA) during ventilation with an inspired oxygen concentration of 100%.

A 14-gauge catheter was then placed in the right pleural space for introduction of air and sampling. A chest x-ray was obtained after placement to exclude any pneumothorax caused by lung injury by the catheter. Arterial blood gas analysis was done to assess any change in $P\mathrm{o}_2$, which also would indicate injury to the lung at the time of catheter placement. After lung injury had been excluded, air (150 cc) was injected into the pleural space through the 14-gauge catheter to create a pneumothorax, and the catheter was then closed. Ventilation with 100% oxygen was continued for 5 min (fresh gas flow 4 litre min^{-1}). Animals were then studied in two phases.

During the control phase, the fresh gas flow was changed to oxygen (2 litre min^{-1}) and nitrous oxide (2 litre min^{-1}). Samples of gas (10 ml) were taken from the pleural space catheter, every 1–2 min. The aspirated samples were analysed with an Ohmeda Rascal II anesthetic gas monitor. To prevent loss of volume from sampling each volume of gas taken was replaced with 10 ml of room air. The concentration of nitrous oxide in the pleural space was recorded against time. After the control measurements (normal circulation) animals were ventilated with 100% inspired oxygen until no nitrous oxide was detected in the pleural space (re-equilibration).

Each animal was then exsanguinated via the femoral arterial cannula until cardiac arrest occurred. I.v. pentobarbital was then administered. This may have been ineffective because cardiac arrest had already occurred but was done to ensure death of the animals, as suggested by our institutional animal studies committee. Ventilation was continued, and gas administration repeated as an experimental phase, with no circulation. After re-equilibration with 100% oxygen, animals were again ventilated with a mixture of nitrous oxide (2 litre min^{-1}) and oxygen (2 litre min^{-1}). Samples of pleural gas were taken and analysed as in the control phase.

Data were analysed using repeated measures analysis of variance (Statistica, Tulsa, OK, USA). The null hypothesis was rejected if $P<0.05$.

Results

Blood gas values did not change after catheter placement

During the control phase (pre-cardiac arrest), a significant ($P<0.05$) increase in concentration of nitrous oxide in the pleural cavity occurred, with a mean concentration of 39.6% nitrous oxide at 6 min. At the conclusion of the control phase, when the F_{IO_2} was increased to 1.0, the concentration of nitrous oxide in the pleural space rapidly declined to mean value of 2.83% nitrous oxide (Fig. 1B, $P<0.05$).

During the experimental phase in the absence of circulation, the concentration of nitrous oxide in the pleural space again increased significantly ($P<0.05$) from zero to a maximum of 42.6% nitrous oxide (mean). This increase resembled that seen in the control group. When F_{IO_2} was changed to 1.0, the nitrous oxide concentration in the pleural space rapidly decreased to 1.5% (mean nitrous oxide concentration) (Fig. 1B).

Discussion

This study suggests that nitrous oxide diffuses directly from alveolar gas into the pleural space rather than being transferred by the circulation. Relatively few studies[1–3] have examined the mechanism of transfer of an insoluble gas to an air filled cavity. Those reports have stated that introduction of the gas into the cavity is secondary to vascular delivery, proposing that the vascular deliver of a relatively soluble gas such as nitrous oxide into the cavity occurs at a faster rate than the relatively insoluble gas nitrogen can be removed. This has been given as the primary explanation for the rapid increase in volume of a pneumothorax observed clinically. In a landmark paper published in *Anesthesiology* 1968, Eger and colleagues[2] proposed that high blood flow to the pleura delivered nitrous oxide to the pleural cavity, resulting in a rapid increase in the concentration of nitrous oxide and in the size of a pneumothorax.

Our study questioned whether the major mechanism of nitrous oxide transfer into the pleural cavities was a result of direct diffusion or vascular delivery. We found a rapid increase in the nitrous oxide concentration in the pleural space in both the control and the experimental animals. We ensured that the samples were not samples from the lung by chest x-ray and blood gas measurement to document absence of pneumothorax caused by lung injury by the pleural catheter.

An increase in nitrous oxide concentration *in the control phase* could potentially be explained by vascular delivery of nitrous oxide to the cavity. However, the increase in nitrous oxide concentration seen when there was no circulation but continued ventilation can only be explained by direct diffusion of nitrous oxide across the visceral pleural surface.

An increase in the size of a pneumothorax in a patient on positive pressure ventilation receiving a gas mixture containing nitrous oxide, is well known clinically. We did not measure the change in volume of the pneumothorax in this study, but the change in volume of the pneumothorax should parallel the increase in nitrous oxide concentration. Based on the results of this study we believe that the rapid increase of nitrous oxide in a pneumothorax is by direct diffusion from the alveoli, independent of vascular delivery.

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Inhibition of active sodium absorption leads to a net liquid secretion into *in vivo* rabbit lung at two levels of alveolar hypoxia

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Active sodium transport across alveolar epithelium is known to contribute to the resolution of pulmonary oedema. We have attempted to assess whether sodium transport is essential to prevent liquid accumulation in healthy pulmonary alveoli exposed to mild hypoxia, and whether its contribution to liquid absorption differs between mild and moderate levels of hypoxia. In twenty-four anaesthetized adult rabbits we used direct bronchial cannulation to measure liquid movement from the liquid-filled left lung over 3.5 h. Half of the rabbits were studied at a level of mixed venous (and alveolar) oxygen partial pressure, $P\bar{v}_{O_2}$, of 6.5 kPa and half at 4.5 kPa. $P\bar{v}_{O_2}$ was altered by changing the inspired oxygen fraction in the ventilated right lung. Alveolar hydrostatic pressure was 0.3 kPa. In each group of 12, six animals with inhibitors of sodium transport in the isosmotic instillate were compared with six controls. We have shown an alveolar liquid secretion (approximately 0.6 μl min^{-1} (kg body weight)$^{-1}$) in the presence of inhibitors of active transport and an absorption (approximately 4 μl min^{-1} (kg body weight)$^{-1}$) in controls. Changing $P\bar{v}_{O_2}$ had no influence on these movements. We conclude that, in this model of pulmonary oedema, active sodium transport appears to be essential for prevention of alveolar liquid accumulation via secretion. Furthermore, the contribution of active sodium transport to liquid absorption remains constant at oxygen tensions between 4.5 and 6.5 kPa.

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Before the discovery of active sodium transport in adult lungs, investigators had managed to convince themselves that passive forces alone could account for healthy alveoli remaining free from large quantities of liquid.[1] Active sodium transport has now been shown to contribute to the clearance of pulmonary oedema in many species including humans.[2] [3] Recently, Verghese and colleagues[4] studied 65 patients with severe hydrostatic oedema in an attempt to identify the importance of such transport in the presence of a presumed intact alveolar epithelium. Using measurements of protein concentration in sequential oedema samples, they concluded that 75% of their patients showed active liquid clearance, that intact active liquid clearance was associated with a more rapid improvement in arterial oxygenation, and that the maximal capacity of the uninjured human lung actively to transport oedema fluid was much higher than had previously been estimated from *ex vivo* studies. It remains unclear whether active sodium transport is necessary for maintenance of liquid balance in the healthy lung.

Alveolar sodium transport can be inhibited both *in vitro* and *in vivo* by the delivery to the alveolar epithelium of amiloride, an inhibitor of apical sodium channels, and phloridzin, an inhibitor of apical sodium–glucose cotransport.[2] The reduction of this transport using ouabain, an inhibitor of the basolateral sodium–potassium ATPase (Na,K-ATPase) that drives the process, is limited to *in vitro* preparations, because of its systemic effects.[5] Although it has proved possible to study the fatal pulmonary effects of elimination of sodium channels in genetically modified mice,[6] selective inhibition of the sodium transport mechanism over the whole alveolar surface in adult animals still ventilated with gas has not proved feasible. In this study, we have utilized gentle complete liquid filling of the apnoeic left lung of the anaesthetized rabbit to deliver amiloride and phloridzin to the apical surface of the alveolar epithelium, and thereby assess the contribution of sodium transport to liquid flux across the healthy epithelium *in vivo*. This model has been validated previously.[7]

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With reference to epithelial cell culture studies, Bärtsch[8] has recently suggested that insufficiency of active alveolar sodium transport may contribute to the aetiology of high altitude pulmonary oedema (HAPO), because of the possible susceptibility of a transport mechanism requiring ATP to the effects of hypoxia. Suzuki and colleagues[9] have shown that exposure of rats to a hypoxic environment of 10% oxygen for 48 h impaired transalveolar liquid transport, but that this impairment was related to a decrease in Na,K-ATPase activity, not a reduction in the availability of ATP. Conversely, Sznajder and colleagues[10] found that exposure of rats to a hyperoxic environment of 85% oxygen for 7 days led both to an upregulation of Na^+ channels and to an increase in Na,K-ATPase activity. In experiments on *in situ* perfused lungs from sheep aged 6 weeks to 6 months, Junor and colleagues found no correlation between the rate of lung liquid absorption and the oxygen partial pressure (P_{O_2}) in the lungs in the approximate range 6–66 kPa during acute experiments lasting approximately 1 h.[11]

Alveolar P_{O_2} in climbers breathing air at the summit of Everest has been estimated to be 4.7 kPa, with the associated mixed venous P_{O_2} being approximately 2.8 kPa.[12] It remains uncertain whether acute exposure of the alveolar epithelium to moderate levels of hypoxia impairs liquid absorption associated with active sodium transport.

In this study we compared absorption over 3.5 h at lung P_{O_2} values of approximately 6.5 and approximately 4.5 kPa to compare the effects of mild and moderate acute hypoxia on liquid movements, with and without inhibition of sodium transport. This enabled us to examine the hypothesis that active epithelial sodium transport is required to prevent net alveolar liquid secretion, and to examine whether transepithelial liquid flows differ between mild and moderate levels of hypoxia.

Methods

Overview

In 24 anaesthetized adult New Zealand White rabbits (2.5–4.1 kg), the left lung was filled with liquid via a bronchial catheter, and subsequently the pressure at the external port of the catheter, which lay at the level of the maubrium, was maintained constant at 0.3 kPa for a period of 6 h. After approximately 100 min, a steady state was achieved, during which measurement of the gradual flow of liquid into, or out of, a reservoir connected to the bronchial catheter permitted direct measurement of transepithelial volume flux. In half of the animals the pulmonary instillate contained inhibitors of each of the two postulated main apical pathways for epithelial sodium transport (amiloride 1 mM to inhibit sodium channels; phloridzin 1 mM to inhibit sodium–glucose cotransport). The other half of the animals acted as controls, in which the instillate contained no drugs. Two different partial pressures of oxygen were achieved in the left lung of two groups of 12 animals by ventilating the right lung with an inspired oxygen fraction ($F_{I_{O_2}}$) of either 1 or 0.3. It was, therefore, possible to study *in vivo* transepithelial pulmonary liquid flux at mild and moderate levels of lung hypoxia, with and without an inhibition of active sodium transport in the alveolar and airway epithelium.

Anaesthesia, monitoring, and surgical preparation

All procedures were licensed by the UK Home Office. Surgery was performed under halothane anaesthesia following premedication with Hypnorm (fentanyl 0.315 mg ml^{-1}, fluanisone 10 mg ml^{-1}; Janssen, UK) 0.3 ml kg^{-1} body weight i.m. Maintenance of anaesthesia during the 6 h study period was achieved by Hypnorm infusion (0.5–1.0 ml h^{-1}) at which time neuromuscular block was achieved with alcuronium 0.5–1.0 mg h^{-1}. Adequacy of anaesthesia was assessed by observing heart rate, arterial pressure, pupil size, and the presence or absence of tears. Tracheostomy was performed and a 4.0 or 4.5 mm internal diameter tracheal tube was introduced into the trachea. Animals breathed oxygen with 1–2% halothane during surgery, and were then ventilated with $F_{I_{O_2}}$ 1 or 0.3 without halothane during the study period. Monitoring included arterial pressure and blood gases (via a carotid artery catheter), ECG and heart rate, limb pulse oximetry, urine output, and rectal temperature. A 4-French gauge cannula was introduced via the left jugular vein into the pulmonary artery for monitoring pulmonary artery pressure (PAP) and sampling mixed venous blood. Cardiac output (Q_t) was measured after 6 h of liquid filling of the left lung using the Fick principle for oxygen; for this purpose apnoeic oxygen uptake measurements for the whole animal were made at the same time at which arterial and mixed venous blood samples were obtained for estimation of blood oxygen concentrations.[13] Pulmonary shunt fraction was estimated from the same blood gas measurements, using the standard alveolar gas equation to estimate alveolar P_{O_2}.

Hartmann's solution (Na^+ 131 mM, K^+ 5 mM, Ca^{2+} 2 mM, Cl^- 111 mM, lactate 29 mM) was infused via an ear vein at 5 ml kg^{-1} h^{-1}. We have previously shown that this animal preparation is stable, in so far as that cardiac output remains constant over 6 h.[14]

Ventilation of the right lung

After neuromuscular block, both lungs were ventilated using a Bear Cub infant ventilator (Bear Medical Systems, Riverside, CA, USA). The ventilator setting was initially: gas flow 8 litre min^{-1}, peak pressure 2 kPa, positive end-expiratory pressure 0.3 kPa, I:E ratio 0.5, $F_{I_{O_2}}$ 1, rate 14–20 min^{-1}. Throughout the experiment, including the 6 h study period, during which only the right lung was ventilated, the ventilator rate was adjusted to maintain arterial carbon dioxide partial pressure (Pa_{CO_2}) between 4.7 and 6.0 kPa, with the other ventilator variables unchanged. Mean airway pressure remained at 0.6–0.7 kPa. $F\text{I}_{O_2}$ was held at 1 in all animals until 150 min after instillation of liquid into the left lung. At this time, in 12 animals $F\text{I}_{O_2}$ was switched to 0.3; in the other 12 animals $F\text{I}_{O_2}$ remained 1 throughout.

Bronchial isolation and liquid filling of the left lung

A balloon-tipped catheter was introduced into the left main bronchus no further than 1 cm from the carina. Correct positioning was achieved by observing chest movements, auscultation, blood gas sampling, and measurement of oxygen flow through the catheter in relation to the measured oxygen uptake of the whole animal. Confirmation of positioning was seen at post-mortem.

Using this catheter, we were able to estimate what fraction of the animal's total lung tissue was present in the left lung (V_{LL}). We did this by holding the animal apnoeic for a few minutes and measuring the separate flows of oxygen during apnoea into the left and right lungs. We assumed that the relative fractions of tissue in the two lungs would be the same as the relative flows of oxygen into the two lungs during apnoea. The purpose in measuring V_{LL} was that the left and right lungs of the rabbit are of different sizes, and interpretation of transepithelial liquid flows, and of lung blood flows, are most usefully made in relation to the proportion of lung tissue studied.

Using the bronchial catheter, the left lung was filled over 1–2 min with a solution of glucose 10 mM and blue Dextran 1 mM that was made isotonic with the animal's plasma using sodium chloride. Plasma and instillate osmolarity were measured by freezing point depression. Amiloride and phloridzin were added in 12 animals (see above). The volume of instillate injected equalled the volume of the left lung at a pressure of 0.3 kPa measured by helium dilution, and the rate of injection was chosen to equal the rate of oxygen uptake measured for the lung, in order to achieve complete liquid filling of the left lung without allowing either atelectasis or overdistention of the lung to occur. After filling the lung with liquid, the bronchial catheter was connected to a reservoir of instillate, the surface of which was kept at a height of 3 cm above the manubrium for 6 h to maintain a constant distending pressure of 0.3 kPa. The reservoir was marked to allow measurements of volumes as small as 0.01 ml; time was measured to the nearest second. Pleural leakage and atelectasis were excluded at post-mortem by inspection of the lung and pleural cavity to confirm that blue Dextran had been homogeneously distributed throughout, and contained within, the lung. Leakage of instillate past the bronchial catheter was excluded at post mortem by confirming that blue Dextran was retained within the study lung.

The volume of liquid that had flowed into, or out of, the left lung was measured every few minutes over 6 h. A steady flow was reached in all animals after approximately 100 min. It is assumed that the non-steady flow during the initial 100 min resulted from changes in lung volume consistent with the known difference in lung compliance between gas-filled and liquid-filled lungs.[15] The results we present are the liquid uptakes over the period 200–360 min, which we take to be direct measurements of transepithelial liquid flux.

Statistical analysis

All data are presented as mean (SEM). One-way analysis of variance (ANOVA) was used to assess whether measurements in the four groups of animals could be regarded as from the same normal distribution. Student's *t*-tests were used to compare between-group means. Significance was regarded as present at $P < 0.05$.

Table 1 Mean (SEM) blood gas variables, pulmonary artery pressure (PAP), cardiac output ($\dot{Q}_t$), shunt fraction, fractional volume associated with left lung (V_{LL}), estimated left lung blood flow ($\dot{Q}_{LL}$), and plasma and instillate osmolarities for four groups of six animals subjected to liquid filling of the left lung for 6 h. $F\text{I}_{O_2}$ is the oxygen fraction ventilating the right lung. 'Inhibitors' refers to the presence in the instillate of inhibitors of epithelial sodium transport. All data are averages of measurements taken every 15 or 30 min during the period 200–360 min after the initial filling of the left lung with instillate, except the readings of cardiac output, which were taken at time 360 min. *P* values refer to one way ANOVA of the four groups of animals (see Statistical analysis)

	Control		**Inhibitors**		
$F\text{I}_{O_2}$	**1**	**0.3**	**1**	**0.3**	*P* (ANOVA)
N	6	6	6	6	
Pa_{O_2} (kPa)	42.9(2.1)	8.8(0.5)	32.7(3.4)	8.5(0.6)	0.000
Pa_{CO_2} (kPa)	5.0(0.2)	5.1(0.1)	5.2(0.3)	5.0(0.2)	0.944
pH_a	7.35(0.02)	7.36(0.02)	7.32(0.03)	7.34(0.02)	0.651
$P\bar{v}_{O_2}$ (kPa)	6.5(0.2)	4.7(0.3)	6.7(0.2)	4.7(0.2)	0.000
$P\bar{v}_{CO_2}$ (kPa)	6.2(0.3)	6.2(0.1)	6.4(0.3)	6.1(0.3)	0.912
pH_v	7.32(0.02)	7.34(0.02)	7.30(0.02)	7.32(0.02)	0.462
PAP (kPa)	2.01(0.19)	2.00(0.07)	1.65(0.12)	1.93(0.12)	0.281
$\dot{Q}_t$ (ml min^{-1} kg^{-1})	200(12)	168(19)	193(9)	201(25)	0.526
Shunt fraction	0.20(0.01)	0.33(0.02)	0.25(0.02)	0.35(0.04)	0.006
V_{LL}	0.37(0.04)	0.43(0.03)	0.36(0.04)	0.37(0.01)	0.538
$\dot{Q}_{LL}$ (ml min^{-1} kg^{-1})	40(3)	55(7)	49(4)	81(15)	0.033
Plasma osmol (mosmol litre^{-1})	284(3)	288(7)	288(5)	294(2)	0.633
Instillate osmol (mosmol litre^{-1})	284(3)	288(7)	289(5)	294(1)	0.651

Table 2 Liquid uptake (µl min^{-1} (kg body weight) $^{-1}$) from the liquid-filled left lung for each animal in the study. There are no significant differences between liquid uptakes at low and high values of $F\mathrm{I}_{O_2}$

	Control				**Inhibitors**			
$F\mathrm{I}_{O_2}$		1		0.3		1		0.3
	Rabbit no.		Rabbit no		Rabbit no.		Rabbit no.	
	4	4.12	2	4.60	18	–0.94	7	–1.42
	5	9.33	3	3.90	21	–0.61	17	–1.08
	10	0.76	6	6.44	29	–0.62	22	0.32
	13	2.58	8	3.44	30	–0.80	24	–0.25
	14	3.17	32	0.91	35	0.115	31	–1.51
	16	5.40	41	4.64	38	–0.20	37	–0.654
Mean		4.23		4.00		–0.51		–0.76
SEM		1.10		0.68		0.15		0.22

Results

All animals survived the 6 h study period and had liquid filling of the left lung confirmed post-mortem. No leakage occurred past the bronchial catheter. .

Initial filling of the left lung with liquid was associated with a rapid decrease in $P\mathrm{a}_{O_2}$ from approximately 55 kPa during oxygenation of both lungs to approximately 15 kPa, followed by a gradual increase until approximately t=150 min. During the period 200–360 min, all physiological measurements changed little, and consequently we report means for this whole period of measurements taken at 15 or 30 min intervals. Table 1 shows arterial and mixed venous blood gases, PAP, $Q\mathrm{t}$, and shunt fraction in the four groups of six subjects. Also shown for each group is the fractional tissue volume (V_{LL}) associated with the left lung as estimated by the fractional apnoeic oxygen uptake measured for the left lung in comparison with the whole animal. Cardiac output measurements were taken only at the end of the period 200–360 min. P values in Table 1, derived from ANOVA, confirm that $P\mathrm{a}_{O_2}$, $P\bar{\mathrm{v}}_{O_2}$, and shunt fraction could not be regarded as from one normally distributed population.

Ventilation with $F\mathrm{I}_{O_2}$ 0.3 was associated with a significantly lower $P\mathrm{a}_{O_2}$ and $P\bar{\mathrm{v}}_{O_2}$ in both control animals and animals with inhibitors of sodium transport in the instillate. Pulmonary shunt fraction was substantially and significantly higher in the groups with $F\mathrm{I}_{O_2}$=0.3. Left lung blood flow was estimated for individual animals by multiplying cardiac output (at 360 min) by the average shunt for the period 200–360 min, and is presented as Q_{LL} in Table 1. As with the pulmonary shunt fraction, Q_{LL} in the four groups could not be regarded as from one normally distributed population. In all four groups plasma instillate osmolarities were very closely matched to plasma osmolarities (Table 1).

In Table 2 are presented the liquid uptakes from the alveoli for the period 200–360 min for each animal. A positive liquid uptake represents a movement of liquid out of the alveoli, that is a net absorption by the alveolar or airway epithelium; a negative liquid uptake represents secretion by the epithelium. The mean (SEM) values for the four groups are presented graphically in Figure 1 in relation to $P\bar{\mathrm{v}}_{O_2}$. In control animals there was a net uptake across the alveolar epithelium of approximately 4 µl min^{-1} (kg body weight)$^{-1}$. This uptake was independent of $F\mathrm{I}_{O_2}$, and hence $P\bar{\mathrm{v}}_{O_2}$. In the presence of inhibitors of sodium transport, the epithelium became secretory with a net uptake of approximately –0.6 µl min^{-1} (kg body weight)$^{-1}$. In the presence of inhibitors of sodium transport, there was no significant difference between the magnitude of the liquid secretion between low and high oxygen groups.

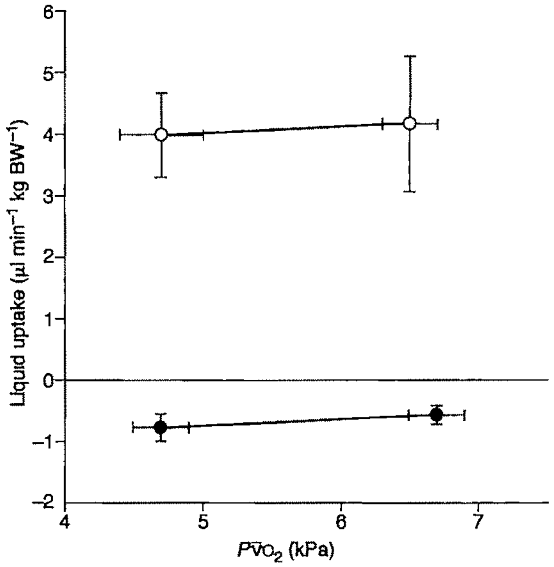

Fig. 1. Liquid uptake by pulmonary epithelium as a function of mixed venous oxygen tension for the liquid-filled left lung of the rabbit in four groups of six animals. Closed circles are for animals with amiloride and phlorizin (inhibitors of apical sodium transport) in the instillate, open circles are for controls. Data are liquid flows measured for the period 200–360 min after initially filling the lung with liquid. The difference between the upper and lower lines is assumed to be the absorptive contribution of active sodium transport. There are no significant differences between liquid uptakes at low and high values of $P\bar{\mathrm{v}}_{O_2}$.

Discussion

The main finding of this study is that active sodium transport reverses a secretion of liquid into the airway tree to generate a net absorption of liquid when the airway hydrostatic pressure is 0.3 kPa in the *in vivo* rabbit lung. Moreover, the liquid flows, with and without inhibition of active sodium transport, are the same at mild and moderate levels of alveolar hypoxia. Our observations provide some evidence that active sodium transport across the pulmonary epithelium may be essential in health, as well as during established pulmonary oedema, to prevent gradual accumulation of liquid within the lung.

Condition of the animals within this study

Data from Table 1 suggest that animals were maintained in a state of good physiological health despite the 6 h duration of the study period and preceding preparation time, both under continuous general anaesthesia. Arterial pH, Pa_{CO_2}, and cardiac output are close to reference values for unanaesthetized animals.[16 17] Arterial oxygen partial pressures did not decrease to values that are associated with severe tissue hypoxia and acidosis. Previous studies using this model have observed a stable preparation over 6 h.[13 14]

Maintenance of alveolar dryness during health

The extent to which the adult lung requires sodium transport to maintain alveoli relatively free from liquid remains to be established.[18] A method has yet to be found of selectively switching off this function of the alveolar epithelium in order to assess its effects on lung liquid balance. Early evidence that sodium transport might contribute to recovery from pulmonary oedema came in 1990 from Matthay and Weiner-Kronish[19], who measured protein concentrations in oedema fluid aspirated from the lungs of patients before, and after, 12 h of intensive therapy. In those patients showing a clinical improvement, the protein concentration increased significantly by 47%, whereas in those patients showing no improvement the protein content changed little. It is likely that active sodium transport was rendered ineffective in the patients who were unable to concentrate protein in oedema fluid, possibly because an increase in alveolar solute permeability led to a loss of the normal balance of Starling forces across the alveolar epithelium.

In the rat lung, the experiment of Basset and colleagues [2] produced a result that suggested that loss of sodium transport leads to alveolar flooding. In the presence of amiloride and phloridzin in alveolar instillate in isolated-perfused lung, they measured a small, but statistically insignificant secretion into the alveoli, suggesting that the lung would continually fill with liquid derived from perfusate unless sodium transport reversed the direction of liquid flux. In the experiment of Vejlstrup and colleagues[7], using a similar preparation to that used in this study, it was observed that alveolar flooding was induced by inhibition of active sodium transport unless alveolar hydrostatic pressure was elevated above 0.4 kPa, a figure commonly used as a mean airway pressure during ventilation of patients with positive end-expiratory pressure.

Unfortunately, the evidence alluded to above, and in the present study, is limited to lungs that are partially or completely filled with liquid before the measurement of absorption or secretion of liquid across the epithelium lining the airway tree. As there continues to be much uncertainty regarding the disposition of liquid within the alveoli of the healthy lung,[20] it is difficult to make predictions for the initiation and intensification of pulmonary oedema in a normal gas-filled lung from studies in which fluxes and pressures have been obtained in the presence of large volumes of liquid. It remains uncertain, for example, whether any liquid lying within a healthy alveolus is bounded by a surface that is concave or convex towards the gas in that alveolus. Consequently, it remains unclear whether surface tension at any liquid–gas interface generates a pressure within such liquid that is lower or higher than atmospheric, lower values tending to exacerbate the formation of oedema, and higher values tending to lead to its resolution. Nevertheless, the observation in this study that even an airway hydrostatic pressure of 0.3 kPa in the lung with inhibitors of sodium transport is insufficient to prevent continuing secretion of liquid into the airway, suggests that the healthy air-filled lungs with an airway pressure close to zero are susceptible to the initiation of oedema if sodium transport is removed.

Contribution of airway chloride secretion to transepithelial liquid flows

The upper airways are normally lined with a film of mucous lying on top of a watery sol that bathes the airway cilia, the maintenance of which appears to be a balance between chloride secretion and sodium absorption; this balance is disturbed in cystic fibrosis.[21] In our study, measurements of absorption from, and secretion into, the airway tree are necessarily the sum of fluxes in the upper and lower airways. It is, therefore, likely that a component of the secretion we observe after inhibiting sodium uptake is the movement of liquid in response to chloride secretion. However, the marked variation of this secretion with alveolar hydrostatic pressure seen in the experiments of Vejlstrup and colleagues[7] suggests that the passive movement of liquid under the influence of Starling forces plays a large role in determining the precise magnitude of the secretion that results after inhibiting sodium transport. Widdicombe and Widdicombe[21] estimate the magnitude of the airway secretion in humans to be 14 ml day^{-1}, that is 0.14 μl min^{-1} (kg body weight)$^{-1}$ for a 70 kg adult. This is about one-fifth of the secretory flows measured in this study following inhibition of sodium transport (0.51 and 0.76 μl min^{-1} (kg body weight)$^{-1}$, Table 2). We know of no more precise data with the help of which it would be possible to compare the relative magnitudes of chloride secretion over the relatively small area of the upper airway with alveolar secretion as a result of passive Starling forces across the huge area of the alveolar-capillary membrane.

Contribution of sodium absorption to transepithelial liquid flows

The component of liquid flux that we attribute to active sodium transport is the difference between the two near horizontal lines in Figure 1. It equals 4–5 μl min^{-1} (kg body weight)$^{-1}$. This figure should be regarded as a lower limit, as inhibition of sodium transport may have been incomplete at the doses of amiloride and phloridzin used. In rat lungs, cross-perfused with blood from a donor rat, Basset and colleagues[2] measured a liquid uptake attributable to active transport of approximately 0.17 μl s^{-1}. The rats used weighed 0.3 kg, which gives a rate of uptake for two lungs of 33 μl min^{-1} (kg body weight)$^{-1}$. Many studies have involved instillation of quite small volumes of liquid into gas-ventilated lungs;[3] consequently, measured fluxes have referred to uncertain fractions of the alveolar surface. However, measurements in several species are broadly similar to those obtained in this study, and suggest that in humans[22] sodium transport may generate a liquid uptake of the order of 1 litre day^{-1}.

Contribution of pulmonary vascular tone to lung liquid balance

Pulmonary capillary pressure is thought to influence liquid flow across the capillary endothelium and, according to the degree of buffering and lymphatic drainage provided by the interstitium, to influence liquid flow across the alveolar epithelium as well.[1] The observation that transepithelial liquid flows, in both the presence and absence of inhibitors of sodium transport, remained unchanged as $P\bar{v}_{O_2}$ was lowered (Fig. 1) suggests that pulmonary capillary pressure is not altered within the range of $P\bar{v}_{O_2}$ studied.

The most commonly accepted explanation for the occurrence of oedema during hypoxic exposure, such as that occurring at high altitude, is that pulmonary microvascular pressure increases and that this increase leads to alveolar flooding. The increase is envisaged as either within fairly small areas of lung as a result of *local failure of arterial* hypoxic vasoconstriction that permits transmission of a high PAP to some capillaries, or more widely throughout the lung as a result of *the presence of venous* hypoxic constriction.[23] Evidence for constriction of pulmonary veins during hypoxia has come from *in situ* dog lung perfusion studies by Welling and colleagues[24] and from myograph studies on rat pulmonary veins by Zhao and colleagues.[25] Conversely, there is evidence for the rabbit that hypoxia leads to a decrease in pulmonary capillary pressure. In the isolated rabbit lung, Sanchez de Léon and colleagues found that hypoxic pulmonary vasoconstriction resulted in a reduction in liquid filtration rate from the vasculature during constant flow perfusion in a forward direction, and an increase in filtration rate during perfusion in a reverse direction from vein to artery.[26] Such a finding suggests that there is not only arterial hypoxic constriction, but that there is a degree of venous hypoxic dilatation, as a constant flow across a constant or increased venous constriction would lead, respectively, to no change or to an increase in capillary pressure.

We have previously shown[14] in this animal model both that there is a slow component of hypoxic pulmonary vasoconstriction that continues to intensify after 150 min, and that during the time period 200–360 min blood flow diversion from the hypoxic left lung does not conform to the widely accepted model of hypoxic constriction of Marshall and colleagues that was derived from short experiments on rats and dogs lasting approximately 10 min.[13 27] In brief, blood flow to the liquid-filled left lung is substantially (approximately 50%) higher when FI_{O_2} to the right lung is 0.3 than when it is 1 (Table 1), whilst the model of Marshall and colleagues predicts that it should be slightly (approximately 7%) smaller.[13] In view of the absence of a significant difference in PAP between these groups, our data suggest that lowering $P\bar{v}_{O_2}$ from 6.5 to 4.5 kPa in the one lung results in a large *decrease* in vascular resistance in that lung, with no change in capillary pressure. Whether this response is entirely a result of the local effect of the lung PO_2, or is at least in part because of pulmonary innervation or humoral factors in the intact animal remains unclear, although arterial hypoxaemia appears to be insufficient to activate the chemoreflex vasodilatation in the lung observed by Levitzky.[28]

Our experiments were performed with a lung PO_2 close to the P_{50} of 5.3 kPa for the hypoxic response in the rabbit in short experiments performed by Weissmann and colleagues.[29] In claiming this, we are assuming that the PO_2 of the apnoeic immobile lung tissue (and hence the alveolar PO_2) was determined primarily by the PO_2 of the blood arriving with a relatively high flow in the pulmonary artery ($P\bar{v}_{O_2}$) rather than the systemic arterial PO_2 of blood arriving with a much lower flow via the bronchial circulation. Noting the result of Weissman and colleagues, we anticipated that the rate of change of pulmonary vascular resistance in the study lung, with respect to changes in $P\bar{v}_{O_2}$, would be greatest at values of $P\bar{v}_{O_2}$ around 5.3 kPa, and thus be most likely to induce a change in liquid flux across the pulmonary epithelium. Indeed, a measured hydraulic conductance of the epithelium in this animal model[7] of 15.7 μl min^{-1} (kg body weight)$^{-1}$ kPa $^{-1}$ suggests that changes of capillary pressure as small as 0.1 kPa might be readily be detected by our measurements of liquid flux with an SEM of 0.15–1.10 μl min^{-1} (kg body weight)$^{-1}$ (Table 2). It seems likely that the capillary pressure changed by less than 0.1 kPa during the change in $P\bar{v}_{O_2}$ of 2 kPa induced in the experiments reported here.

In summary, we have observed a *vasodilatation* in the study lung on lowering $P\bar{v}_{O_2}$ from 6.5 to 4.5 kPa that has permitted a large increase in blood flow, but that has probably induced little or no change in the hydrostatic pressure across the alveolar-capillary structures, including the pulmonary interstitium. In future studies of this type, interpretation of the relationship between pressure and flow across the alveolar-capillary structures would be aided by obtaining histology of the lung to understand the extent to which interstitial oedema and lymphatic drainage might contribute to a difference between flows across the pulmonary capillary endothelium and the alveolar epithelium.

Independence of liquid flow associated with active sodium transport from $P\bar{v}_{O_2}$

Given that active sodium transport may be necessary to maintain the fluid balance of the healthy lung, the hypothesis of Bärtsch[8] that inhibition of this process by hypoxia might lead to pulmonary oedema clearly needs to be considered. At the simplest level, it is conceivable that a process requiring ATP as fuel might fail at low levels of P_{O_2}. It has recently become apparent, however, that a wide range of both short-term and long-term physiological responses are regulated by hypoxia via the transcriptional regulator hypoxia-inducible factor 1.[30] It seems possible that a reduction in alveolar liquid clearance by hypoxia lasting 48 h,[9] and increase in alveolar liquid clearance by hyperoxia lasting 7 days,[10] may be regulated by a system of this type. Experiments on ion transport in fetal rat distal lung epithelial cells by Ramminger and colleagues[31] have shown time-dependent effects of raising P_{O_2} from 23 to 100 mm Hg on different components of the sodium transport system. At 24 h an increase in sodium pump activity was measured, but 48 h was required to induce an increased abundance of the sodium channel protein α-ENaC. An increase in sodium pump activity was measured at 3 h, but only became significant beyond 6 h.[31] The experiments reported here suggest that 3 h are not sufficient for a change from mild (6.5 kPa) to moderate (4.5 kPa) alveolar hypoxia to induce a decrease in active sodium transport across the *in vivo* rabbit alveolar epithelium.

Conclusion

In conclusion, the present study suggests, first, that active sodium transport across alveolar epithelium is essential to prevent alveolar flooding in the healthy lung. A second finding is that moderate hypoxia lasting a few hours appears not to worsen pulmonary oedema, either by inhibiting active sodium transport, or by raising capillary hydrostatic pressure.

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One MAC of sevoflurane provides protection against reperfusion injury in the rat heart *in vivo*

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Volatile anaesthetics protect the heart against reperfusion injury. We investigated whether the cardioprotection induced by sevoflurane against myocardial reperfusion injury was concentration-dependent. Fifty-eight α-chloralose anaesthetized rats were subjected to 25 min of coronary artery occlusion followed by 90 min of reperfusion. Sevoflurane was administered for the first 15 min of reperfusion at concentrations corresponding to 0.75 (n=11), 1.0 (n=11), 1.5 (n=13), or 2.0 MAC (n=12). Eleven rats served as untreated controls. Left ventricular peak systolic pressure (LVPSP, tipmanometer) and cardiac output (CO, flowprobe) was measured. Infarct size (IS, triphenyltetrazolium staining) was determined as percentage of the area at risk. Baseline LVPSP was 131 (126–135) mm Hg (mean (95% confidence interval)) and CO 33 (31–36) ml min^{-1}, similar in all groups. During early reperfusion, sevoflurane reduced LVPSP in a concentration-dependent manner to 78 (67–89)% of baseline at 0.75 MAC (not significant *vs* controls 99 (86–112)%), 71 (62–80)% at 1 MAC (P<0.05), 66 (49–83)% at 1.5 MAC (P<0.05) and 56 (47–65)% at 2 MAC (P<0.05). CO remained constant. While 0.75 MAC of sevoflurane had no effect on IS (34 (27–41)% of the area at risk) compared with controls (38 (31–45)%, P=0.83), 1.0 MAC reduced IS markedly to 23 (17–30)% (P<0.05). Increasing the concentration to 1.5 MAC (23 (17–30)%) and 2 MAC (23 (13–32)%, both P<0.05 *vs* controls) had no additional protective effect. One MAC sevoflurane protected against myocardial reperfusion injury. Increasing the sevoflurane concentration above 1 MAC resulted in no further protection.

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Sevoflurane protects against reperfusion injury after myocardial ischaemia *in vitro*[1 2] and *in vivo*.[3] Sevoflurane like isoflurane has only minimal cardiovascular effects.[4] Compared with other anaesthetics,[5] depression of myocardial contractility lowers with sevoflurane. However, all previous studies investigating the effects of volatile anaesthetics against reperfusion injury used only one anaesthetic concentration. In isolated rat hearts, 1.5 MAC (minimum alveolar concentration) of sevoflurane reduced creatine kinase release and improved myocardial function;[2] in rabbits, 1.0 MAC sevoflurane reduced infarct size after regional myocardial ischaemia and reperfusion.[3] It remains unknown, whether the cardioprotective effect of sevoflurane is concentration-dependent.

Therefore, we investigated the effects of four different concentrations of sevoflurane on myocardial reperfusion injury after occlusion of a major branch of the left coronary artery in rats *in vivo*.

Materials and methods

The study was performed in accordance with the regulations of the German Animal Protection Law and was approved by the Bioethics Committee of the District of Düsseldorf.

Animal preparation

Fifty-eight Wistar rats (body weight mean 486 (95% confidence interval, 479–493) g) were anaesthetized by intraperitoneal pentobarbital 60 mg kg^{-1}. After intubation of the trachea, the lungs were ventilated (Rhema-Labortechnik Beatmungsgerät, Typ 10ml, Cass 34931, Germany) with a tidal volume of 5 ml at 60 breaths min^{-1} to maintain $P\text{CO}_2$ within physiological limits. Surface electrocardiogram (Siemens Elema AB EKG-Gerat, Germany) was recorded continuously. After cannulation of the femoral vein, the rats received a single dose of α-chloralose (50 mg kg^{-1}). For compensation of fluid losses and maintenance of anaesthe-

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sia, saline 0.9% (5 ml h^{-1}), and α-chloralose (25 mg kg^{-1} h^{-1}) were infused continuously. For measurement of aortic pressure, a polyethylene catheter was inserted into the descending aorta via the femoral artery and connected to a pressure transducer (Statham, PD23, Gould, Cleveland, OH, USA).

After median sternotomy and pericardiotomy were performed, an ultrasonic flowprobe was placed around the pulmonary artery in order to measure cardiac output (CO, 6S ultrasonic flowprobe, T 208, Transonic Systems Inc., Ithaca, NY, USA). A ligature snare was passed around a major coronary artery for later occlusion. Left ventricular (LV) pressure (LVP) was monitored using a catheter tip manometer (Millar Microtip-Catheter Model SPR-407, size 2F, Houston, TX, USA) advanced from the right carotid artery via the aortic arch into the left ventricle. A temperature probe was placed sub-diaphragmatically (GTH 1160, Digital Thermometer, Geisinger Electronic, Germany) and body temperature was maintained constant at 38.8 (0.3)°C by adjusting a heating pad and a warming lamp.

Experimental programme

After 15 min of recovery from surgical preparation, baseline measurements were performed. Tightening the snare around the prepared coronary artery induced myocardial ischaemia. The effectiveness of this manoeuvre was verified by the appearance of epicardial cyanosis and changes in surface ECG. After 25 min of occlusion, the snare occluder was released and successful reperfusion was verified by the disappearance of epicardial cyanosis. During the initial reperfusion period (first 15 min), the rats inhaled sevoflurane in different concentrations. After 90 min of reperfusion, the hearts were quickly excised and mounted on a modified Langendorff perfusion system for determination of infarct size.

Eleven rats underwent the ischaemia-reperfusion programme without further intervention and served as controls. In 47 rats, sevoflurane was added to the inspired gas starting 1 min before reperfusion to achieve a stable concentration at the beginning of the reperfusion period. The anaesthetic was then continued for the first 15 min of reperfusion. The volatile anaesthetic was titrated to an end-tidal concentration (Datex Capnomac Ultima, Division of Instrumentarium Corp., Helsinki, Finland) of 1.8 (0.75 MAC; n=11), 2.4 (1 MAC, n=11), 3.6 (1.5 MAC, n=13), and 4.8 vol.% (2 MAC, n=12), respectively. An end-tidal concentration of 2.4% corresponds to 1.0 MAC of sevoflurane in rats.[6]

Measurement of infarct size

Hearts were perfused on a modified Langendorff apparatus with normal saline at 80 mm Hg perfusion pressure to wash out any remaining blood. The coronary artery was then re-occluded and 5–10 ml of 0.2% Evans Blue dye in 1% dextrane was infused via the aortic root into the coronary system. This manoeuvre identifies the area at risk as unstained. The heart was then frozen and cut into 8–15 transverse slices of equal thickness (1 mm). The slices were incubated (37°C) for 15 min in buffered 1% triphenyltetrazoliumchloride adjusted to pH 7.4 and then incubated for 2 days in 4% formaldehyde. Viable myocardium was then identified as red stained by triphenyltetrazoliumchloride, whereas necrotic myocardium appears pale grey. The area at risk and the infarcted area were determined by planimetry using Sigma Scan Pro 5 computer software (SPSS Science Software) and corrected for dry weight.

Data analysis

LVP, its first derivative dP/dt, aortic pressure and CO were recorded continuously on a polygraph (Hellige 120 710 94, Freiburg, Germany) and were digitized using an analogue to digital converter (Data Translation, Marlboro, MA, USA) at a sampling rate of 500 Hz and processed later on a personal computer.

Haemodynamic variables

Global systolic function was measured as LV peak systolic pressure (LVPSP) and the maximum rate of pressure increase (dP/dt_{max}). Global LV end-systole was defined as the point of minimum dP/dt and LV end-diastole as the beginning of the sharp upslope of the LV dP/dt tracing. Systemic vascular resistance (SVR) was calculated from mean aortic pressure and CO, assuming a right atrial pressure of 0 mm Hg in the open-chest preparation.

Statistical analysis

Data are presented as means and 95% confidence interval. Statistical analysis was performed by a two-way analysis of variance (ANOVA) for time and treatment (sevoflurane concentration) effects. Time effects (changes from baseline value) were analysed by using Dunnett's post-hoc test. If an overall significance between groups was found, comparison was made for each time point using one-way ANOVA followed by the Dunnett's post-hoc test where appropriate.

Results

Sixty-four rats were used. Six rats died from ventricular fibrillation during coronary artery occlusion. In the remaining 58 animals, complete data sets were obtained.

Haemodynamic function

Figure 1 shows a recording of the haemodynamic variables during a single experiment. During baseline conditions, no between group differences in haemodynamics were observed (data are summarized in Table 1 and Fig. 2). Coronary artery occlusion resulted in a reduction of LVPSP, dP/dt_{max} and SVR to 91 (85–96)% of baseline values, 94

(87–102)%, and 83 (79–88)%, respectively. They were similar in all groups (data at 23 min ischaemia). CO remained constant (99 (95–104)%), and LV end-diastolic pressure increased to 182 (155–208)%.

During reperfusion, no further changes from ischaemic values were observed in controls, except for a further reduction in SVR to 83 (71–96)% of baseline. Sevoflurane slightly reduced heart rate during the early reperfusion

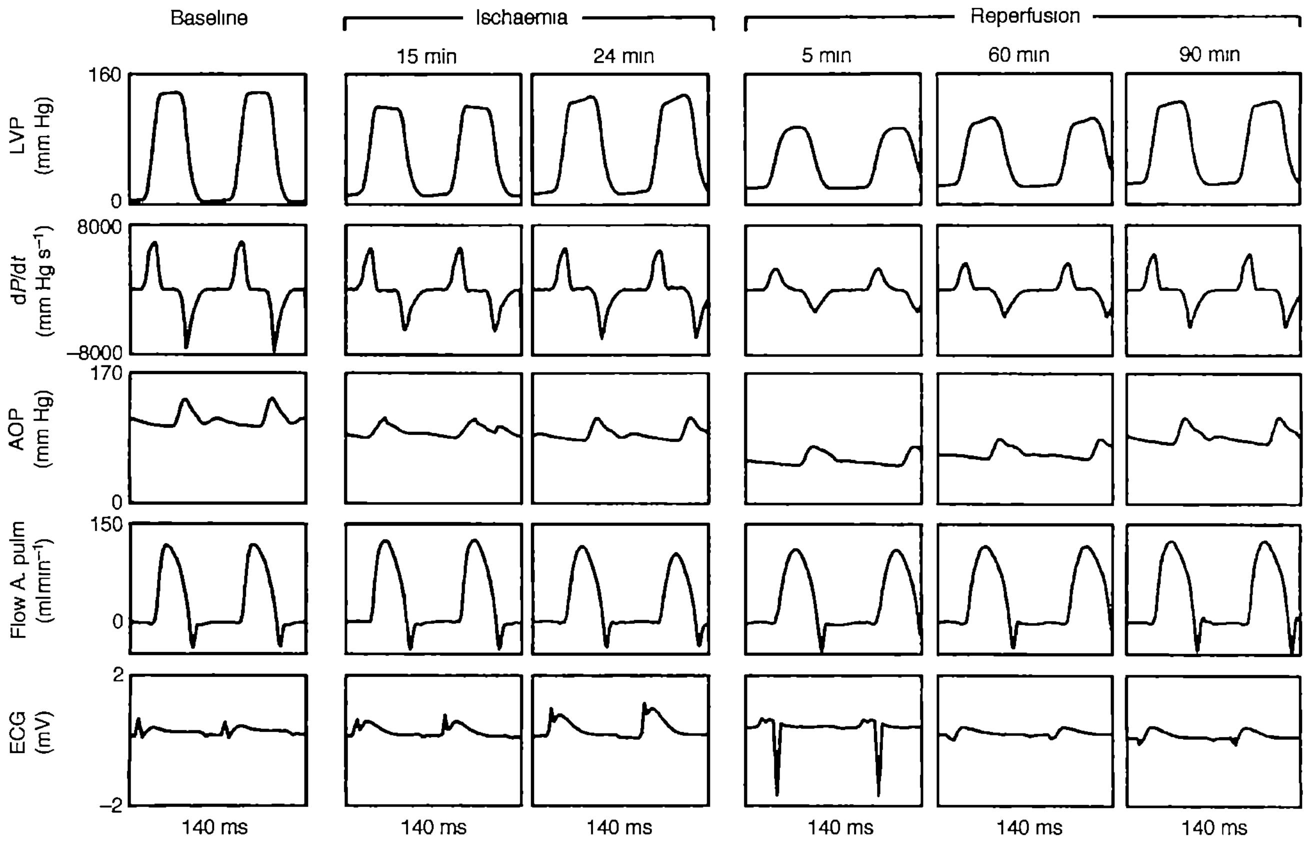

Fig 1 Registration showing selected times from one experiment where 1 MAC sevoflurane was given during initial reperfusion. LVP=left ventricular pressure, d*P*/d*t*=rate of change of LVP, AOP=aortic pressure, Flow A pulm =pulmonary artery flow, ECG=electrocardiogram

Table 1 Haemodynamic variables during ischaemia-reperfusion experiments (% changes from baseline) in the control group and the groups receiving 0 75 (0 75 MAC), 1 (1 MAC), 1.5 (1 5 MAC), and 2 MAC (2 MAC) of sevoflurane Data are mean (95% confidence interval) *P<0 05 *vs* controls, †P<0 05 *vs* baseline

	Coronary artery occlusion			**Reperfusion**			
	Baseline	**15 min**	**24 min**	**5 min**	**15 min**	**30 min**	**90 min**
LVEDP	(mm Hg)	(%)	(%)	(%)	(%)	(%)	(%)
Control	10 (7–12)	163 (143–183)	171 (141–203)	184 (139–229)	160 (134–188)	153 (117–189)	147 (103–192)
0 75 MAC	10 (5–15)	162 (110–214)	167 (110–214)	189 (120–259)	177 (117–236)	155 (124–186)	129 (83–175)
1 MAC	9 (7–11)	165 (130–200)	176 (129–223)	196 (129–263)	188 (119–257)	202 (134–270)	198 (133–263)
1 5 MAC	9 (7–11)	205 (147–264)	237 (167–307)	229 (165–292)	227 (166–288)	244 (175–312)	228 (130–326)
2 MAC	10 (7–12)	158 (122–194)	169 (134–205)	168 (134–202)	169 (140–198)	163 (129–196)	168 (138–198)
dP/dt_{max}	(mm Hg s^{-1})	(%)	(%)	(%)	(%)	(%)	(%)
Control	6845 (5794–7897)	105 (87–123)	108 (89–126)	103 (84–123)	102 (79–124)	103 (79–126)	110 (81–139)
0 75 MAC	6222 (5444–7001)	92 (81–103)	105 (86–125)	75 (63–86)*†	74 (57–91)*†	98 (84–111)	99 (85–113)
1 MAC	6972 (5643–8301)	95 (84–107)	91 (79–104)	66 (54–78)*†	61 (48–74)*†	81 (69–93)	77 (60–95)
1 5 MAC	7584 (6532–8636)	101 (74–128)	102 (65–138)	59 (38–80)*†	52 (32–72)*†	81 (52–110)	82 (52–112)
2 MAC	6736 (5482–7990)	80 (66–94)	81 (67–94)	46 (37–55)*†	43 (34–52)*†	71 (56–86)	73 (53–93)*
CO	(ml min^{-1})	(%)	(%)	(%)	(%)	(%)	(%)
Control	32 (27–37)	102 (90–114)	102 (90–114)	108 (99–117)	107 (98–116)	112 (101–124)	114 (95–133)
0 75 MAC	30 (26–34)	103 (90–116)	104 (88–119)	109 (91–128)	104 (89–120)	114 (103–125)	114 (96–133)
1 MAC	35 (27–42)	95 (88–101)	97 (89–105)	102 (89–115)	101 (90–111)	100 (92–107)	99 (82–116)
1 5 MAC	37 (32–42)	104 (92–116)	99 (83–114)	92 (93–111)	88 (64–112)	64 (86–103)	100 (83–118)
2 MAC	34 (26–41)	92 (84–100)	93 (82–103)	89 (76–103)	86 (70–101)	94 (81–108)	90 (73–106)

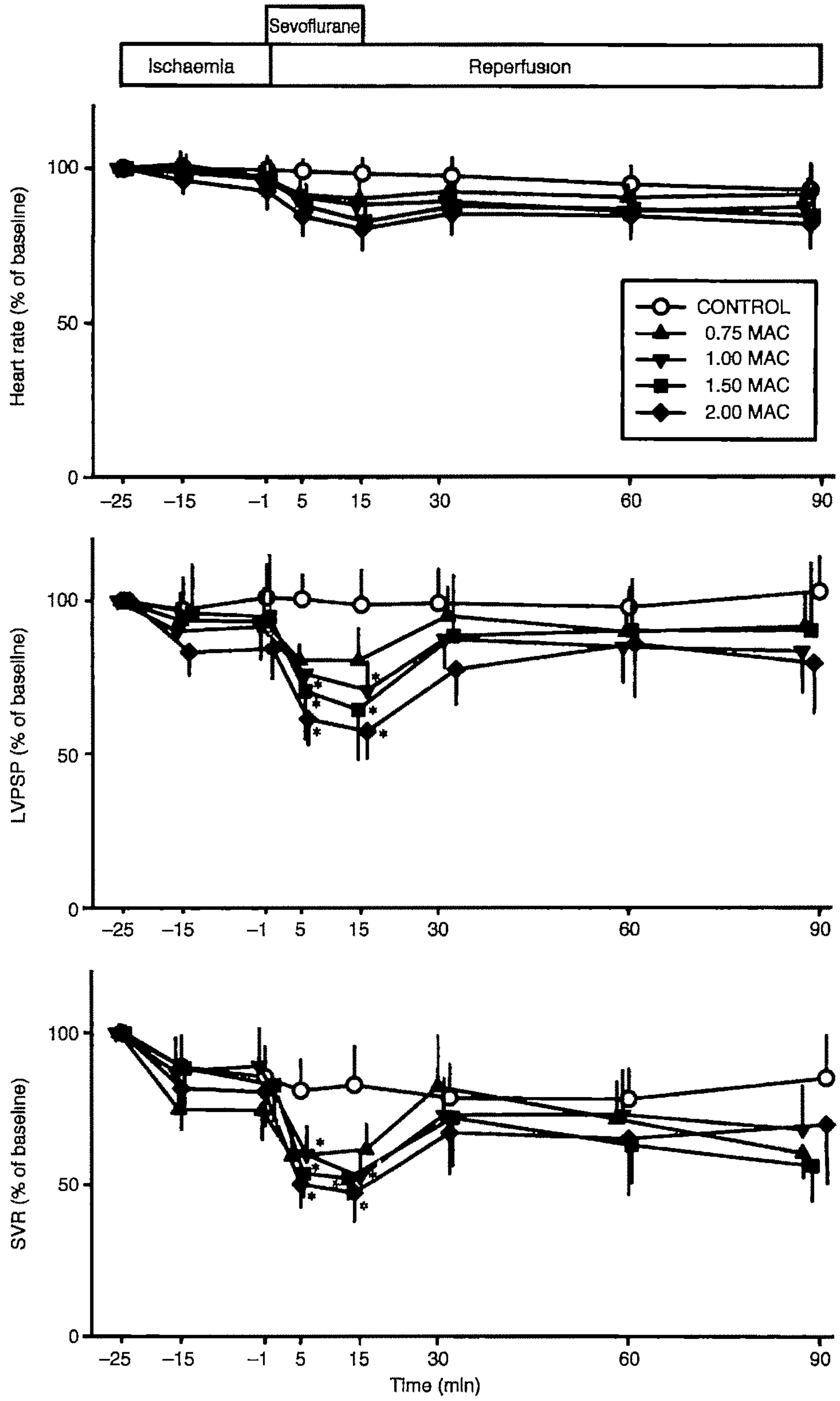

Fig 2 Line plot showing the time course of heart rate (HR), left ventricular peak systolic pressure (LVPSP) and systemic vascular resistance (SVR) during the experiments (data are mean (95% confidence interval), $^{*}P<0.05$ *vs* baseline). LVPSP and SVR decreased in a concentration-dependent manner during initial reperfusion, but no differences between the treatment groups were observed at the end of the experiments Baseline values were: HR (beats min^{-1}): controls, 441 (413–467); 0.75 MAC, 431 (407–456); 1 MAC, 443 (423–452); 1.5 MAC, 444 (426–462), 2 MAC, 441 (412–470) LVPSP (mm Hg): controls, 125 (112–138), 0.75 MAC, 130 (122–137), 1 MAC, 132 (120–144); 1.5 MAC, 135 (126–144), 2 MAC, 129 (116–142) SVR (mm Hg ml^{-1} min): controls, 3.2 (2.6–3.8), 0.75 MAC, 3.7 (3.2–4.2); 1 MAC, 3.5 (3.0–4.1); 1.5 MAC, 3.3 (2.8–3.7), 2 MAC, 3.5 (2.7–4.3)

period (P<0.05 *vs* baseline, Fig. 2). A concentration-dependent depression of LVPSP to 56 (47–65)% (P<0.05 *vs* controls) with 2.0 MAC was observed after 15 min of sevoflurane administration (Fig. 2). A similar reduction was seen for dP/dt_{max} (to 43 (34–52) %; P<0.05 *vs* controls, Table 1) and SVR (to 48 (38–57)%; P<0.05 *vs* controls, Fig. 2). Administration of sevoflurane had no effect on CO (99 (87–102)% of baseline) after 15 min of reperfusion.

Infarct size

Mean heart dry weight was 0.19 (0.18–0.21) g with no differences between groups (data for the individual groups are given in Table 2). Ischaemic-reperfused area (area at risk) constituted 28 (24–31)% of the total heart size. In controls, infarct size was 38 (31–45)% of the area at risk (Fig. 3). Infarct size was reduced by 1 MAC sevoflurane to 23 (17–30)% of the area at risk (P<0.05). Increasing the sevoflurane concentration had no further effect on infarct size reduction: 1.5 MAC, 23 (17–30)%; 2 MAC, 23 (13–33)% of the area at risk (both P<0.05 *vs* controls). However, a lower concentration of sevoflurane (0.75 MAC) had no effect on infarct size (0.75 MAC, 33 (27–41)% of the area at risk, P=0.83 *vs* controls).

Table 2 Heart weight and area at risk size in the control group and the groups receiving 0.75 (0.75 MAC), 1 (1 MAC), 1.5 (1.5 MAC), and 2 MAC (2 MAC) of sevoflurane. Data are mean (95% confidence interval)

Group	Heart weight (g)	Area at risk (% of heart weight)
Control	0.19 (0.17–0.21)	29 (21–38)
0.75 MAC	0.18 (0.17–0.20)	32 (21–43)
1 MAC	0.19 (0.17–0.22)	26 (20–31)
1.5 MAC	0.19 (0.18–0.20)	23 (16–30)
2 MAC	0.21 (0.15–0.27)	28 (20–37)

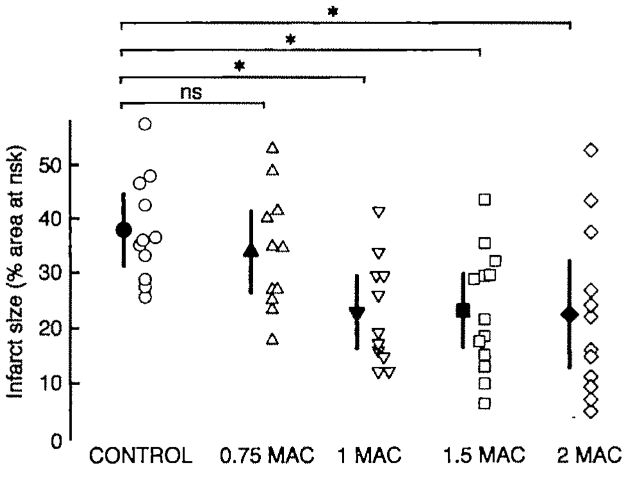

Fig 3 Infarct size expressed as per cent of the area at risk. Open symbols represent single data points, filled symbols are mean and 95% confidence interval, *P<0.05.

Discussion

Reperfusion injury characterizes a situation in which the myocardium loses viability by pathological mechanisms that are triggered by restoration of oxygen and substrate supply after myocardial ischaemia.[7] This type of myocardial cell damage is caused by mechanisms which take place during reperfusion and not during the preceding ischaemia.

Inhalation anaesthetics offer specific protection against myocardial reperfusion injury in a variety of experimental settings.[1 8–10] For sevoflurane, it was shown that a concentration corresponding to 1.5 MAC reduced creatine kinase release and improved myocardial function after global ischaemia in isolated rat hearts.[1] In addition, 1.5 MAC sevoflurane provided further protection against reperfusion injury even if the heart was already protected against the ischaemic damage using a cardioplegic solution.[2] Sevoflurane at a concentration corresponding to 1 MAC reduced infarct size after regional ischaemia in rabbits *in vivo*.[3] No data concerning concentration-dependent effects of sevoflurane or other anaesthetics against myocardial reperfusion injury are available.

The present study demonstrates that 1 MAC sevoflurane reduces infarct size after regional ischaemia in the rat heart *in vivo*. A lower concentration (0.75 MAC) has no effect on infarct size. Increasing the concentration of sevoflurane to 2 MAC produced a similar reduction of infarct size as 1 MAC sevoflurane. However, during administration of these higher concentrations, more pronounced haemodynamic side effects were observed.

One mechanism responsible for the phenomenon of early reperfusion injury was first described in isolated cardiomyocytes as the 'oxygen paradox'. The hypoxic-reoxygenated cells developed cellular hypercontracture during reoxygenation, resulting in cytolysis.[11] This hypercontracture is caused by simultaneous resupply of ATP after reactivation of oxidative phosphorylation and uncontrolled Ca^{2+}-release from the sarcoplasmic reticulum, leading to uncontrolled cellular contraction. For halothane, a protection against hypercontracture was demonstrated by an action on the Ca^{2+}-dependent Ca^{2+}-release channel of the sarcoplasmic reticulum.[12] One might speculate that the interaction between this channel and volatile anaesthetics follows a ligand-binding kinetic. This would result in a dose-dependent effect of the volatile anaesthetics, with no further increase in protection after blocking all channels. However, volatile anaesthetics might have different effects on sarcoplasmic Ca^{2+}-handling[13–15] and actions of sevoflurane on these channels are not known. Therefore, it remains speculative whether the observed maximal protection with 1 MAC of sevoflurane results from a specific effect at this channel.

In the intact animal, haemodynamic effects during reperfusion might also influence the amount of infarcted tissue. For example, a reduction of myocardial afterload[16 17] or a staged reperfusion[18–20] (in contrast to a sudden reperfusion) might reduce reperfusion injury. Despite significant necrosis, control hearts showed no changes in LVPSP or CO (Fig. 2, Table 1). This finding can be explained by the mass of the infarcted tissue, which constituted 38 (31–34)% of the area at risk, but only 7.5 (6.2–8.8)% of the total ventricular mass. Taking into account that the large potential increase in CO during exercise, it is not surprising that a 7.5% decrease of the contractile mass can be compensated for without major changes in haemodynamics.

Haemodynamic effects of volatile anaesthetics are known to be concentration-dependent. Sevoflurane caused a significant reduction of SVR and only a small reduction in heart rate. A reduction of SVR does not necessarily reduce CO, and a reduced heart rate can be compensated for by an increase in stroke volume, resulting in maintained CO (Table 1, Fig. 1). There was a more pronounced reduction in LVPSP during reperfusion with the higher concentrations of sevoflurane in our experiments (Fig. 2). In contrast, infarct size was no further reduced by higher concentrations of sevoflurane. Therefore, it is likely that specific actions of sevoflurane on reperfused myocardium rather than haemodynamic changes are responsible for the observed reduction in infarct size. These results are in line with previous findings that the action of volatile anaesthetics on reperfusion injury is independent of haemodynamic changes.[9]

In addition to direct effects at the myocardium and haemodynamic alterations, interactions with leukocyte activation and accumulation may also reduce reperfusion injury. By plugging capillaries, leukocytes may play an important role in the 'delayed no-reflow phenomenon',[21] resulting in persistent ischaemia. Sevoflurane (0.5–1.0 MAC) has been shown to attenuate adhesion of neutrophils and platelets in the coronary system after ischaemia and reperfusion.[22–25] As a result, changes in regional myocardial blood flow could occur. Myocardial blood flow was not measured in the present study and it cannot be excluded that alterations of endo- or epicardial blood flow contributed to the protection against reperfusion injury by sevoflurane. Activation of leukocytes results in release of oxygen-derived free radicals, which can further increase cellular damage. Sevoflurane also reduced the production of radicals as well as the damage caused by free radicals.[24]

Reperfusion of ischaemic myocardium may occur in a variety of clinical situations, for example after coronary artery bypass surgery. In cardio-compromised patients, optimal protection against myocardial reperfusion injury in the absence of haemodynamic side effects might be beneficial. We demonstrated that 1 MAC of sevoflurane protects against ischaemia-reperfusion injury in the rat heart *in vivo* and that increasing the concentration further did not improve cardioprotection, but increased the cardiodepressant side effects.

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BJA

REVIEW ARTICLE

The new neuromuscular blocking agents: do they offer any advantages?

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The introduction of neuromuscular blocking drugs in 1942 marked a new era in anaesthetic and surgical practice. The anaesthetist was enabled to provide respiratory support during long and complex surgery whilst the surgeon was allowed access to body cavities without voluntary or reflex muscle movement. In recent years, a generation of anaesthetists trained since atracurium and vecuronium became available in 1982, have taken for granted the speed of onset, shorter and more predictable duration of action, and lack of cardiovascular side-effects that these drugs have in comparison with their predecessors.[56 58 59] The latest generation of neuromuscular blocking drugs aims to provide even greater advantages: as rapid an onset and offset as succinylcholine; disposition independent of organ function; and minimal adverse effects.

New neuromuscular blocking drugs

Since atracurium and vecuronium, the benzylisoquinolinium diesters, mivacurium and the 1R *cis*–1′R *cis* isomer of atracurium, cisatracurium, have become available for clinical use. The aminosteroid, rocuronium, became available in 1995. Another aminosteroid, rapacuronium (Org 9487) (Fig. 1), became available in the USA in 1999, although it was withdrawn from the market by Organon Teknika in spring 2001, for reasons which are detailed below (see Adverse events: Respiratory, p. 920). The search for other series of compounds with non-depolarizing neuromuscular blocking properties presently centres on the bis-tetrahydroisoquinolinium chlorofumarates,[17] and the tropinyl diester derivatives.[50] The most promising of the first group seems to be the asymmetrical mixed-onium chlorofumarate, GW280430A[10] (Fig. 2), which has been tested in both animal and human studies. The bis-quaternary ammonium salt of bistropinyl diester G-1-64 is the most studied of the tropinyl diester group[51] although investigations in humans have yet to be reported (Fig. 3).

GW280430A

The structure of this mixed-tetrahydroisoquinolinium chlorofumarate is given in Figure 2. The similarity in structure to mivacurium is demonstrated. The presence of three methyl groups between the quaternary nitrogen and oxygen atom at each end of the carbon chain suggests that, similar to mivacurium, this compound will not undergo Hofmann degradation. Little is known as yet about its metabolism. It is said to be degraded by chemical mechanisms *in vitro*.[77] It is possible that the chloride substituted double bond in the carbon chain is its weak point. The molecule appears to be in the *trans–trans* configuration similar to one of the active isomers of mivacurium and in contrast to cisatracurium. It is the *trans* isomers of mivacurium and atracurium that undergo ester hydrolysis.

G-1-64

This is a bis-quaternary ammonium salt of a bistropinyl diester derivative.[51] The molecule was selected from more than 200 tropinyl diester compounds. These agents are characterized by:

1. A connecting chain of acid diesters attached to the C3 atom of two tropine molecules.

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†**Declaration of interest:** Over 3 yr ago, one of the authors, Prof. Hunter, was funded by Organon Teknika to carry out clinical investigations on rapacuronium.

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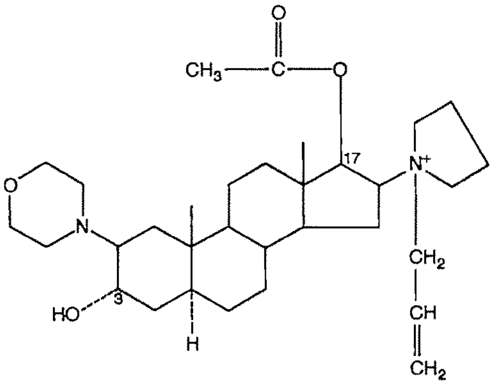
Rocuronium



Rapacuronium

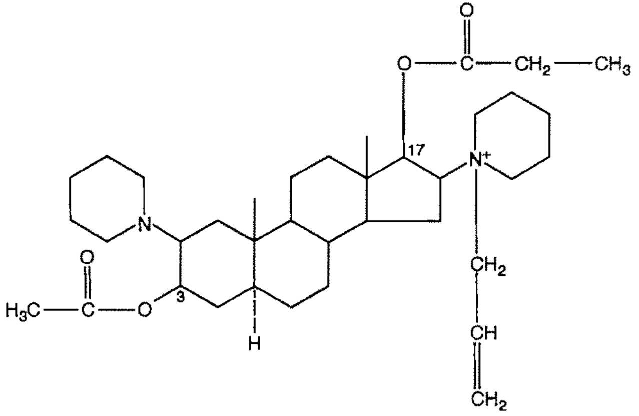


Fig 1 The structure of the aminosteroid neuromuscular blocking drugs, rocuronium and rapacuronium Note the absence of an acetyl (CH_3COO) group at the 3-carbon position on rocuronium. The removal of this acetyl group on rapacuronium and replacement by a hydrogen ion is the first stage in its metabolism to the metabolite Org 9488, which also has neuromuscular blocking properties.

2. Bulky quaternary substitutes on the tropine N atoms.
3. Varying interonium distances between the terminal groups.

G-1-64 is the prototype of this series of compounds, with an interonium distance of 14.74 Å. It is not yet known how this compound is metabolized. Such diesters could be predicted to undergo hydrolysis in the plasma. Another tropinyl diester compound, *N*-(3,4-diacetoxybenzyl)-tropinium-3α-yl] glutarate dibromide (TAAC3), has also undergone investigation in animals and appears to undergo non-organ dependent elimination.[111 112]

Onset of action

Production of neuromuscular block depends on the presence at the post-synaptic nicotinic receptor of sufficient molecules of a neuromuscular blocking drug to produce depolarization of the endplate (depolarizing drugs), or to compete with acetylcholine to prevent it causing depolarization (non-depolarizing drugs). Bowman[19] postulated that speed of onset is inversely related to potency. When a non-depolarizing neuromuscular blocking drug is used, more than 75% of the post-synaptic nicotinic receptors must be occupied to produce clinical signs of neuromuscular block. All the agents we commonly use (even the relatively impotent ones) are sufficiently potent that the vast majority of the drug molecules within the junctional cleft are bound to a receptor. The number of molecules of a neuromuscular blocking drug which must enter the post-synaptic cleft to produce a given degree of block is, therefore, relatively constant. Within a series of compounds such as the aminosteroid or benzylisoquinolinium agents, a less potent drug is given in a higher dose; a larger number of molecules are, therefore, available to diffuse more rapidly into the neuromuscular junction than the smaller number of molecules of a more potent drug. Thus a less potent agent is more likely to produce a more rapid onset of action (Table 1). Compare the most potent benzylisoquinolinium agent, doxacurium ($2{\times}ED_{95}{=}0.05$ mg kg^{-1}), with a time to maximal neuromuscular block of 6 min with the less potent atracurium ($2{\times}ED_{95}{=}0.4$ mg kg^{-1}), which has a much shorter time to maximal block of 2.4 min.

When Boros reported his investigation in rhesus monkeys of a series of bi- and mixed-tetrahydroisoquinolinium chlorofumarates, he found that the inverse relationship between potency and speed of onset of action was maintained.[18] In contrast, in studying a series of neuromuscular blocking tropinyl diesters, Gyermek found that the most potent compounds, those with the longest carbon chain attached to the nitrogen atoms of the bis-quaternary ammonium derivative, produced the more rapid onset of block.[49] Undoubtedly, Bowman did stress that this relationship of potency to onset of block was relevant only to the aminosteroid and benzylisoquinolinium compounds.[19] But Kopman demonstrated that the same effect was evident across these classes of drug with gallamine (a bis-quaternary amine), tubocurarine and pancuronium.[67]

Wright[120] proposed that as well as potency dictating the number of drug molecules available in the plasma to bind to post-synaptic nicotinic receptors and thus impact on onset time, a rapid equilibration between plasma and effect site will increase the rate of onset. Wright calculated that the rate at which the rapacuronium concentration will equilibrate between plasma and the effect site is 2.4 times that of rocuronium and 3.4 times that of vecuronium. He offers this property, perhaps because of the greater lipophilicity of rapacuronium compared with other neuromuscular blocking drugs,[120] as a further explanation for its rapid onset.

ED_{95}

The dose of a neuromuscular blocking drug required to produce 95% twitch depression (ED_{95}) is taken as a guide to the required intubating dose. It is generally considered that at least twice this dose is required to ensure adequate

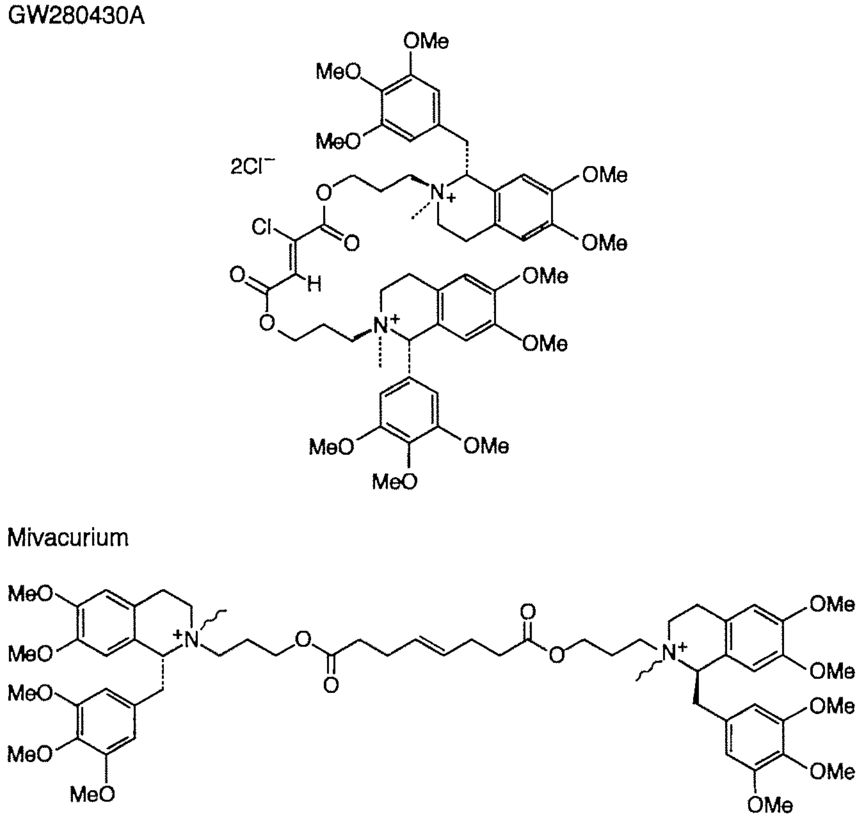


Fig 2 The structure of GW280430A, an asymmetric mixed-tetrahydroisoquinolinium chlorofumarate[17] with four stereogenic centres, two of which are quaternary ammonium, is given The similarity in structure to mivacurium is demonstrated.

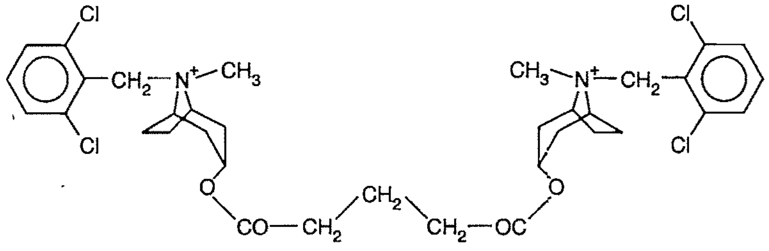


Fig 3 The structure of G-1-64, bis-[*N*-(2,6-dichlorobenzyl) tropanium-3α-yl] glutarate dibromide, which is a bis-quaternary ammonium salt of a bistropinyl diester derivative, with neuromuscular blocking properties

intubating conditions in all patients. The ED$_{95}$ for rapacuronium has been estimated to be 1.0 mg kg^{-1} during established nitrous oxide/oxygen/halothane anaesthesia.[116] Many of the studies comparing rapacuronium with succinylcholine 1.0 mg kg^{-1} have used rapacuronium 1.5 mg kg^{-1},[86 106] or even 2.5 mg kg^{-1},[1] (Table 2). Confusion has arisen from early studies of the ED$_{95}$ of rapacuronium, as results varied according to whether the active moiety or the bromide salt of the drug had been used.[48] Kahwaji has calculated that 1.5 mg kg^{-1} of the active moiety of rapacuronium would be equivalent to 1.7 mg kg^{-1} of the bromide salt.[61] His studies suggest that rapacuronium 1.5 mg kg^{-1} allows intubation to be achieved as easily as with succinylcholine on more than 80% of occasions, whilst doses larger than 1.5 mg kg^{-1} provide conditions equal to those of succinylcholine (Table 2).[61] It is now standard practice with the commercial preparation to refer to the dose of rapacuronium in terms of the active moiety.

Rapacuronium, similar to rocuronium, has a greater range of effect than succinylcholine, making succinylcholine the more predictable drug.[80 119] Many authors have also reported successful rapid sequence intubation in less than 90 s with rocuronium 1.0 mg kg^{-1}.[5 84] This dose is more than three times the ED$_{95}$ of rocuronium and thus is not a valid

Table 1 Time to maximal block of the train-of-four twitch response after approximately twice the ED_{95} (the dose required to produce a 95% reduction in twitch height), of various neuromuscular blocking drugs

Drug	**Dose ($mg\ kg^{-1}$)**	**Time to maximal block (min)**	**Time to 25% recovery (min)**	**Ref.**
Quaternary amines				
Succinylcholine	1.0	0.8	7.6	52
Benzylisoquinoliniums				
Atracurium	0.4	2.4	38	21
Mivacurium	0.15	1.8	16	33, 121
Doxacurium	0.05	5.9	83	7
Cisatracurium	0.1	7.7	46	21, 72
Aminosteroids				
Pancuronium	0.08	2.9	86	63, 87
Vecuronium	0.1	2.4	44	2
Rocuronium	0.6	1.0	43	16
Rapacuronium	1.5	0.9	14.2	52

comparison with rapacuronium 1.5 mg kg^{-1}. Mivacurium and cisatracurium at doses of two to three times the ED_{95} have longer onset times of 2–8 min.[21 33 121]

Belmont has estimated the ED_{95} for the mixed-onium chlorofumarate GW280430A to be 0.19 mg kg^{-1}. Using $3 \times ED_{95}$ in 11 ASA I male volunteers, its onset of action was 1.58 min.[9] Gyermek has administered the bistropinyl diester G-1-64 to rats, rabbits, cats, ferrets, pigs, and monkeys and produced 80–90% neuromuscular block in less than 2 min in each animal using $3 \times ED_{80}$.[51] Although the bistropinyl diesters have not yet been studied in humans, it seems that the speed of onset of these two new groups of non-depolarizing agents may be similar to rapacuronium and rocuronium.

Response of different muscle groups

Variation in the onset and duration of response of different muscle groups to neuromuscular blocking drugs has been well-described.[37] Bragg attributes this difference in response to the effect of varying blood flow to different muscle groups, producing variable times to equilibration at the effect site.[22] Vecuronium,[46] mivacurium,[95] and rocuronium[96] all have a more rapid onset and offset at the laryngeal muscles compared with the adductor pollicis muscle. This differential onset has not been reported for cisatracurium, perhaps because of its higher potency and its longer onset time. Wright and Debaene have both shown a more rapid onset of rapacuronium at the laryngeal muscles than at the adductor pollicis. Wright administered rapacuronium 1.5 mg kg^{-1} and reported a time to maximal neuromuscular block of 0.8 min at the laryngeal adductors compared with 1.0 min at the adductor pollicis.[120] Debaene studied rapacuronium 0.75, 1.5, and 2.0 mg kg^{-1} and recorded the time from the end of injection until the first depression of the first twitch of the train-of-four response (lag time). The lag times at the larynx were 27, 23, and 20 s, respectively, compared with 42, 35, and 31 s, respectively, at the adductor pollicis muscle.[32] Debaene also found a reduced duration of effect of rapacuronium at the laryngeal muscles; he explains this laryngeal resistance by differentiating between the high density of acetylcholine receptors found in the fast contraction laryngeal muscles,[100] and the relatively low receptor density found in the slow fibres of adductor pollicis.[60] Wright[120] suggests that the more rapid onset of rapacuronium at the laryngeal muscles is a result of greater laryngeal blood flow and a more rapid equilibration between compartments with this drug. He offers the latter explanation for the difference between the onset of effect of rapacuronium and other non-depolarizing agents. Wright, however, found no evidence of laryngeal resistance with rapacuronium.

Belmont studied the onset of neuromuscular block produced by GW280430A in the laryngeal muscles and adductor pollicis. In a group of 20 volunteers, he found a more rapid onset at the laryngeal muscles compared with the adductor pollicis at all doses studied (1, 2, and $3 \times ED_{95}$), whilst evidence of laryngeal resistance was only found at the lowest dose used ($1 \times ED_{95}$). Time to 25% recovery T1 was similar in both groups of muscles.[10]

Effect of age

Elderly patients. An increased onset time in elderly patients has been shown with pancuronium, vecuronium, rocuronium, mivacurium, and cisatracurium.[40 29 82 30 93 105] A less dynamic circulation and increased transfer time to the effector site in the elderly are likely explanations for this effect. Ornstein compared the onset time of neuromuscular block produced by cisatracurium 0.1 mg kg^{-1} ($2 \times ED_{95}$) in two groups of patients, aged 30–49 yr and 65–82 yr. He found that mean (SD) onset of block was slower in the older age group, 3.4 (1.0) min against 2.5 (0.6) min in the younger age group.[93] Sorooshian also measured speed of onset of neuromuscular block in younger (34 (9) yr) and older (74 (6) yr) patients given cisatracurium 0.1 mg kg^{-1}. He too found a slower onset of block in the older patients by about 1 min. He calculated the plasma concentration profile of cisatracurium. The predominantly different factor between the two age groups was a reduced rate of effect site equilibration in the elderly, k_{eo} being reduced to 0.06 min^{-1} in the elderly from 0.071 min^{-1} in the young.[105]

In one study[61] comparing intubating conditions in 61 elderly patients (>65 yr) and 120 younger patients (<65 yr) at 60 and 90 s after administration of rapacuronium 0.5–2.5 mg kg^{-1}, no statistically significant differences were found. However, the degree of block was greater in the younger patients at 60 s suggesting that, as for other steroidal neuromuscular blocking drugs, the pharmacodynamic behaviour of rapacuronium may be found to be altered in elderly patients, when adequate numbers have been studied.

Table 2 Studies comparing speed of onset of neuromuscular block at the adductor pollicis muscle and intubating conditions after different doses of rapacuronium and succinylcholine

Drug	Dose (mg kg^{-1})	Anaesthetic technique	Onset (s) (add poll) (SD)	Excellent (%)	Good (%)	Poor (%)	Failed (%)	Ref.
Succinylcholine	1.0	Propofol, nitrous oxide, alfentanil	51					52
Rapacuronium	1.5		54					
Rapacuronium	0.75	Propofol, fentanyl	126 (33)					32
Rapacuronium	1.5		96 (20)					
Rapacuronium	2.0		82 (21)					
Rapacuronium	1.5	Thiopental, fentanyl, halothane, nitrous oxide	96 (1.0)					102
Vecuronium	0.07		203 (46)					
Succinylcholine	1.0	Thiopental, fentanyl		88.3		9.4	2.3	86
Rapacuronium	1.5			85.9		8.6	5.5	
Succinylcholine	1.0	Thiopental and fentanyl or propofol and alfentanil		90.4		7.7	1.9	106
Rapacuronium	1.5			80.6		18.8	0.6	
Rapacuronium	0.5	Propofol, fentanyl, nitrous oxide		10	20	30	40	61
Rapacuronium	1.0			30	30	15	25	
Rapacuronium	1.5			26	42	16	16	
Rapacuronium	2.0			53	37	5	5	
Rapacuronium	2.5			77	23	0	0	
Succinylcholine	1.5	Thiopental		68	21	11	0	1
Rapacuronium	2.5			67	26	7	0	

Younger patients. A more rapid onset of neuromuscular block in children than in adults has been shown for rocuronium, mivacurium, and cisatracurium.[108 23 24] Taivainen gave 20 infants (1–11 months), 20 children (2–12 yr), and 20 adults (20–45 yr), rocuronium 0.15 mg kg^{-1} (1×ED$_{50}$). He recorded onset times of 2.6 (0.5), 1.9 (0.4), and 2.3 (0.5) min in infants, children and adults, respectively.[108] Bryson reviewed several paediatric studies of cisatracurium, each showing a shorter time to maximal block than in similar adult studies.[24] Brandom studied the speed of onset of neuromuscular block produced by a large dose of mivacurium 0.3 mg kg^{-1} (4×ED$_{95}$) in 180 children between the ages of 1 month and 13 yr. The degree of block was measured as a percentage at 90 s. More intense block was obtained in infants than in older children and those with more intense block were more likely to have intubating conditions scored as 'excellent'.[23]

Rapacuronium 0.9 mg kg^{-1} produces 100% block in children in 62 s with no adverse haemodynamic effect.[62] No data have been reported as yet for the chlorofumarates or the tropinyl diesters regarding the effect of age on their pharmacology.

Duration of block

Pharmacodynamics

After a bolus dose of rapacuronium 1.5 mg kg^{-1}, 25% recovery T1 occurs in 10–16 min (Table 4); this is slightly shorter than with mivacurium 0.15 mg kg^{-1} at 16 min.[33] Twenty-five per cent recovery T1 after succinylcholine is even shorter at 8 min.[52] Note that the times to 25% recovery after vecuronium, rocuronium, atracurium, and cisatracurium are all around 40 min following a bolus dose of 2×ED$_{95}$ (Table 1).

Pharmacokinetics

Low potency, a high rate constant for the equilibration of the effect compartment concentration with plasma concentration (k_{eo}), and a rapid clearance are thought to be the required properties of a neuromuscular blocking drug with a fast onset and offset.[14 38 119] Several studies have shown this to be the case for rapacuronium. Wierda,[119] Schiere,[101] and Fisher[45] have all independently calculated the plasma clearance of rapacuronium to be between 7 and 8 ml kg^{-1} min^{-1}; twice the value of 4.0 ml kg^{-1} min^{-1} for vecuronium and rocuronium.[117] Schiere found the plasma equilibration constant (k_{eo}) for rapacuronium to be three times that for rocuronium, at 0.45 and 0.16 min^{-1}, respectively.[101 118] Knowledge of the elimination half-life of a neuromuscular blocking drug is of limited value after use of only a bolus dose as, with the exception of atracurium and cisatracurium, recovery from block occurs during the distribution phase. But after several doses, or an infusion of a neuromuscular blocking drug, when the plasma concentration will be higher, recovery from block may occur during the elimination phase. This variable will then have clinical significance as it takes five elimination half-lives of a drug for the plasma concentration to decrease to almost zero (3% of its original value).

Repeated boluses and infusions

Van den Broek, McCourt, and Schiere have studied the effect of repeated boluses or an infusion of rapacuronium on the duration of neuromuscular block.[110, 83, 102] They found that the duration of block is increased after repeated boluses, and that despite a reduction in dosage to maintain 90–95% twitch depression during an infusion, the duration of block will be almost doubled after the infusion is stopped compared with a single bolus. Two main mechanisms were suggested for this prolonged duration. First, saturation of the redistribution sites and, perhaps more importantly, the effect of the active metabolite of rapacuronium, Org 9488.

Table 3 Time to maximal block of the train-of-four twitch response and time to 25% or 90% recovery T1/T0 for the bis-onium chlorofumarate GW280430A and the bistropinyl diester G-1-64, respectively.[10, 51] [a]Monkey *Macaca cynomolgus* [b]Monkey *Macaca cyclopis* Swinehoe

Species	Dose (mg kg^{-1})	Time to maximal block (min)	Time to 25% recovery (min)
Bis-onium chlorofumarate GW280430A			
Man	0.18	2.6	4.7
Man	0.36	1.7	7.0
Man	0.54	1.5	9.3

Species	Dose (mg kg^{-1})	Time to maximal block (min)	Time to 90% recovery (min)
Bistropinyl diester G-1-64			
Rat	0.92	1.2	6.4
Rabbit	0.093	1.8	6.3
Cat	0.091	2.1	9.8
Ferret	0.062	1.6	10.5
Pig	0.41	1.3	6.5
Monkey[a]	0.3	0.9	4.6
Monkey[b]	0.86	1.3	7.3

Org 9488 is the 3-desacetyl metabolite of rapacuronium and has neuromuscular blocking activity.[101] Schiere estimates that 1% of an ampoule of rapacuronium will contain Org 9488 as an impurity and that 7% of a dose of rapacuronium will be metabolized to Org 9488 after 6 h. Org 9488 has a low clearance of 1.1–1.3 ml kg^{-1} min^{-1},[101] which is one-sixth that of rapacuronium (7.28 ml kg^{-1} min^{-1}), and similar to pancuronium (1.8 ml kg^{-1} min^{-1}).[87] Org 9488 has a k_{eo} of only one-quarter that of rapacuronium, 0.11 and 0.45 min^{-1}, respectively.[101] This active metabolite is produced in the liver and excreted almost entirely in the urine,[101] in contrast to rapacuronium, which is metabolized mainly by the liver.[97] Org 9488 not only has a lower clearance but is continuously being generated after a bolus dose of rapacuronium. Thus, this metabolite may contribute to the delayed recovery from rapacuronium seen after repeated boluses or infusion of the drug.[101]

Chlorofumarates and bistropinyl esters

The mixed-onium GW280430A given to rhesus monkeys, cats, dogs, and male human volunteers has a duration of action of less than 6 min following 1×ED_{95} (0.18 mg kg^{-1} in humans; Table 3); 3×ED_{95} increases the duration of action by approximately 50%.[8, 9, 11, 18, 55] Belmont investigated an infusion of GW280430A (74±11 µg kg^{-1} min^{-1}) titrated to maintain 95–99% neuromuscular block for 120 min in cats. He found that the recovery time (3.6 (0.6) min) after the infusion was discontinued was not prolonged.[8]

Gyermek has studied the duration of action of the bistropinyl diester, G-1-64 in several species of animals and has recorded 90% T1 recovery times of 5–10 min using

Table 4 Time (min) to 25% recovery at the adductor pollicis muscle after a rapacuronium bolus or infusion

Rapacuronium dose (mg kg^{-1})	Anaesthetic technique	Time to 25% recovery (mean: min)	Ref.
Bolus			
1.5	Propofol, alfentanil	16.3	83
1.5	Propofol, alfentanil, nitrous oxide	14.2	52
1.5	Propofol, fentanyl	13.4	120
1.5	Propofol, fentanyl	12.8	107
1.5	Thiopental, fentanyl, nitrous oxide, halothane	10.7	102
0.75	Propofol, fentanyl	5.6	32
1.5		10.2	
2.0		13.9	
2.5	Thiopental	16.9	1
Infusion and bolus			
Bolus 1.5 mg kg^{-1}+0.049 mg kg^{-1} min^{-1} infusion	Thiopental, fentanyl, nitrous oxide, isoflurane	13.4	44
Infusion only			
0.211 mg kg^{-1} min^{-1} infusion	Thiopental, fentanyl, nitrous oxide, isoflurane	11	101

Table 5 The pharmacokinetic variables of the newer neuromuscular blocking drugs

Drug	Plasma clearance (ml kg^{-1} min^{-1})	Volume of distribution (ml kg^{-1})	$t_{1/2}$ beta (min)	k_{eo} (min^{-1})	Ref.
Benzylisoquinoliniums					
Atracurium	6.6	87	21	0.1	43,94
Mivacurium					
cis–cis	5.2	266	53		53
cis–trans	95.0	210	1.8		
trans–cis	70.0	200	1.9		
Doxacurium	2.7	220	99		26
Cisatracurium	5.7	161	24	0.179	31
Aminosteroids					
Vecuronium	4.0	199	108	0.11	79,102
Rocuronium	4.0	270	131	0.16	117
Rapacuronium	7.28	193	88	0.449	101
Org 9488	1.28	233	169	0.105	101,107

an ED_{80} dose of the drug (Table 3).[51] Recovery times are similar after an ED_{90} dose of TAAC3 in dogs and monkeys.[111 112] In his study of the family of bistropinyl diesters, Gyermek found that the more potent compounds were those with the *shortest* duration of action,[49 50] in contrast to the benzylisoquinolinium diesters and the aminosteroids. For instance, the C12 compound has an ED_{50} of 220 $\mu g\ kg^{-1}$ and a recovery index of 1.1 min. In contrast, the much less potent C2 compound, with an ED_{50} of 1340 $\mu g\ kg^{-1}$, has a recovery index of 3.3 min.[49]

Effect of age

Recovery times from pancuronium,[40] vecuronium,[29] and rocuronium[82] are slower in the elderly compared with younger age groups. Kahwaji[61] has studied the effect of dosage and age on the speed of onset and duration of action of rapacuronium. Although he showed a dose dependent increase in duration of block, which was statistically significant in elderly patients, the slower speed of onset, prolongation of block and longer recovery times of any given dose in elderly patients were not statistically significant from younger patients. Szenohradszky[107] and Fisher[44 45] examined the effect of age on the pharmacokinetics of rapacuronium. Szenohradsky found a reduction in clearance of 0.9% per yr of age (compared with 30 yr); Fisher[44] found a reduction in clearance of 0.5% per yr of age (compared with 45 yr). However, in an earlier study, Fisher[45] had found that age had no effect on the clearance of rapacuronium. Fisher[44] attributed the difference in findings between the two studies that demonstrated an effect of age on the clearance of rapacuronium[107 44] and the study which did not,[45] to the smaller number and shorter duration of plasma sampling in his earlier report.

When Sorooshian studied cisatracurium 0.1 mg kg^{-1} in 31 young patients (18–50 yr) and 33 elderly patients (>65 yr) he found no increase in duration of action or recovery times between the age groups.[105] Ornstein investigated cisatracurium 0.1 mg kg^{-1} given to 12 young patients (30–49 yr) and 12 older patients (65–82 yr) and also found no difference in duration of action or recovery times between groups.[93] Dahaba used a dose-adjusted mivacurium infusion to maintain one to two twitches of the train-of-four response in 21 younger patients (18–41 yr) and 20 older patients (64–79 yr). Although he noted a significant reduction in dose requirement in the elderly compared with the younger patients, there was no difference in the recovery index between groups.[30]

Reversal of block

Difficulty with intubation is not always predictable and, therefore, rapid recovery from block is one of the major advantages of succinylcholine. The aim has been to have as rapid a recovery from a non-depolarizing agent. Following administration of succinylcholine 1 mg kg^{-1}, extubation can be achieved after 10–12 min.[57] None of the non-depolarizing agents has a similar spontaneous recovery profile. The early use of a reversal agent after rapacuronium has been investigated to assess whether this drug can be used as a short-acting agent equivalent to succinylcholine in this respect.

Although the first studies of the time course of reversal from rapacuronium induced block found a time to a train-of-four ratio of 0.7 of less than 12 min using neostigmine 0.05 mg kg^{-1},[116] these times have not been replicated by later research.[88 98] Purdy[98] reduced the time to 25% recovery T1 from 16 min to 8–9 min using neostigmine 0.05 mg kg^{-1} or 0.07 mg kg^{-1} given either 2 or 5 min after rapacuronium 1.5 mg kg^{-1}. The time to recovery of the train-of-four ratio to 0.7 was also reduced from 42 min to around 20 min. Hayes,[52] Debaene,[32] Kahwaji,[61] and McCourt[83] have studied recovery when neostigmine 0.05 mg kg^{-1} was given at a later stage after rapacuronium (T1=25%). All these studies were unable to reduce the time from administration of rapacuronium 1.5 mg kg^{-1} to a train-of-four ratio of 0.7 to less than 20 min irrespective of the reversal agent, dose or time of administration.

Lein has studied the reversibility of GW280430A induced neuromuscular block in 16 male volunteers, using 1, 2, and

Table 6 Urinary and biliary excretion of neuromuscular blocking drugs over 24 h[58]

Drug	**Excretion (%)**		**Ref.**
	Urine	**Bile**	
Quaternary Amine			
Succinylcholine	<10	–	58
Benzylisoquinoliniums			
Atracurium	10	–	103
Mivacurium	<10	–	27
Doxacurium	25–30	–	26
Cisatracurium	16		66
Aminosteroids			
Vecuronium	15	40	12
Rocuronium	20	54	109
Rapacuronium	<12	80	101,107

$3\times ED_{95}$ and edrophonium when T1=10%. She found recovery of 25% T1-TOF ratio of 0.9 to be 3 min in each of the three groups,[77] that is, a constant reversal time. Belmont has given GW280430A as a 2-h infusion to cats and found no increase in the recovery index compared with a single bolus of $1\times ED_{95}$.[8] This lack of prolongation of the recovery index with increasing dose suggests that GW280430A is likely to be non-cumulative, consistent with rapid degradation.

Little information is available on the reversal characteristics of G-1-64. Some of the most potent compounds in this family have been reported to have a recovery index (25–75% T1/T0) of less than 2 min in early studies in rats.[49]

New reversal agents

The well-recognized cardiovascular and intestinal side-effects of the anticholinesterases used to reverse residual neuromuscular block has prompted the search for alternative agents. The concept has recently been introduced of the use of *chemical chelation* of neuromuscular blocking drugs at the end of surgery to antagonize block. *Cyclodextrins* are a group of cyclic oligosaccharides, which are recognized to encapsulate lipophilic molecules including steroids. Org 25969 has been investigated in monkeys and been found to antagonize residual block produced by rocuronium more rapidly than neostigmine, without any significant cardiovascular changes.[15]

Hepatic and renal failure

Metabolism and excretion

Rapacuronium has been found to be eliminated mainly by the liver in both human and animal studies,[97] as is vecuronium,[13,97] and rocuronium.[64,97] Less than 12% of a dose of rapacuronium is eliminated in the urine; half is excreted unchanged and half as Org 9488.[101,107] Cisatracurium is cleared predominantly by Hofmann elimination (76.9%) to form laudanosine. Laudanosine is further metabolized to a number of conjugated metabolites which are excreted in the urine.[66] The renal clearance of cisatracurium in health was calculated to be 16% of the total clearance; thus, renal elimination accounts for most of the non-Hofmann (organ) elimination of cisatracurium.[66]

Liver disease

Fisher[44] and Duvaldestin[41] investigated the effect of cirrhosis on the pharmacokinetics of rapacuronium. Fisher studied six cirrhotic patients and found that plasma clearance and steady state volume of distribution were similar to a healthy control group.[44] In contrast, Duvaldestin found a 40% increase in plasma clearance and a 50% increase in the steady state volume of distribution in cirrhotic patients.[41] However, in both studies only a small number of patients were investigated and thus further (larger) studies will be required. No prolongation of the duration of action of rapacuronium was found following a single bolus or a 30-min infusion of the drug in cirrhotic patients.

Van Miert has compared rocuronium in normal patients and those with hepatic failure.[113] He found that although the time to maximal neuromuscular block did not differ between groups, the recovery times were prolonged in the cirrhotic group. The mean times to 25% recovery T1 after rocuronium 0.6 mg kg^{-1} were 53.7 and 42.3 min in the cirrhotic and control group, respectively ($P<0.05$).[113] Khalil[64] and Magorian[81] have also reported delayed recovery from rocuronium in hepatic failure. In van Miert's study, plasma clearance was significantly reduced in the cirrhotic group compared with healthy patients (2.66 *vs* 3.7 ml kg^{-1} min^{-1}) and the elimination half-life was significantly prolonged (143 *vs* 92 min). Steady state volume of distribution was unchanged.[113] In contrast, Khalil and Magorian did not report a reduction in the clearance of rocuronium in cirrhosis.[64,81] Van Miert attributes the differences to the failure of Khalil to normalize the results to take account of body weight; and to the use of a shorter sampling time, a smaller number of patients, and a different pharmacokinetic model in Khalil's study. Van Miert's findings are consistent with the work of Khuenl-Brady in cats.[65]

As renal excretion accounts for approximately three-quarters of the non-Hofmann elimination of cisatracurium, it is not surprising that the effect of this drug is little changed in hepatic failure.[31] After a bolus of cisatracurium 0.1 mg kg^{-1}, volume of distribution was increased by 21% and clearance by 16% in a cirrhotic group, compared with healthy patients. As the major elimination pathway for cisatracurium is organ independent, the increased clearance is probably a result of the larger volume of distribution. The mean (SD) elimination half-life was similar in both groups (26.5 (3.6) and 24.4 (2.9) min, respectively).

Kidney disease

Fisher[44] and Szenohradszky[107] found a 24% and a 32% decrease, respectively, in the clearance of rapacuronium in renal failure, with a reduced dosage required to maintain a target range of neuromuscular block in the pathological state.[44] But they found that the recovery profile after a single bolus or short infusion (30 min) was not affected in renal patients. Szenohradszky reported that 60 min after a single bolus of rapacuronium, plasma concentrations decrease more slowly in patients with renal failure. Plasma concentrations of Org 9488 decrease minimally in this group compared with healthy controls. He postulated that if repeated boluses or a prolonged infusion of rapacuronium were used in renal failure patients, recovery would be delayed. The clearance of the active metabolite of rapacuronium, Org 9488, is 15% of normal in renal failure;[107] this may be the most important factor in the increased duration of effect of rapacuronium in this disease state. Fisher suggests that monitoring neuromuscular block to adjust the dose of rapacuronium may minimize the impact of renal failure on the accumulation of Org 9488.[44]

After rocuronium 0.6 mg kg^{-1}, up to a fifth of the dose is recovered unchanged from the urine within 24 h.[109] After the same dose, Cooper found a 32% reduction in clearance, (2.5 against 3.66 ml min^{-1} kg^{-1}), with an increase in recovery time in chronic renal failure patients compared with a healthy control group.[28]

Eastwood compared cisatracurium 0.1 mg kg^{-1} in 17 patients with end-stage chronic renal failure and 15 healthy patients. He found a 13% reduction in clearance and an increase from 30 to 34 min in the elimination half-life in the renal failure group.[42]

Adverse events

Respiratory

All the studies that have recorded the incidence of adverse events have reported bronchospasm after administration of rapacuronium; it appeared to be more common in smokers and patients with a history of reversible airways disease. Kahwaji,[61] Sparr,[106] Purdy,[98] McCourt,[83] Levy,[75] and Szenohradszky,[107] found bronchospasm in 16 out of 181, 18 out of 167, nine out of 117, four out of 90, seven out of 47, and two out of 20 patients studied, respectively. Thus, bronchospasm was found in more than 9% of patients. Three of these adverse events were classed as serious and required treatment. An incidence of bronchospasm of one in 11 makes rapacuronium significantly different from the other aminosteroids in this respect.

Since rapacuronium became available for clinical use in the USA, a series of case reports published in 2001 has highlighted 21 cases of bronchospasm after its administration, 14 of which were severe.[47] Twenty of the reports occurred in children.[68 85 89] The most concerning feature of these case reports is the severity of the bronchospasm. It was associated with arterial desaturation, difficult or impossible ventilation even following tracheal intubation, and the requirement for i.v. epinephrine. In contrast to the earlier reports, there was no apparent association between the bronchospasm and a history of reversible airways disease. As a result of these reports, the sale of rapacuronium has been suspended by Organon Teknika in the USA.

Newman studied cisatracurium given by infusion to 40 critically ill patients.[92] One of the patients developed mild intermittent bronchospasm during the infusion and for 24 h following its discontinuation. There are few other reports of cisatracurium causing adverse respiratory effects.

Heerdt has studied the effect of GW280430A on the respiratory system of six male beagles; he measured pulmonary artery pressures, peak inspiratory pressure and pulmonary compliance.[54] He found no change in these variables at doses up to $25\times ED_{95}$.

Cardiovascular

Neuromuscular blocking drugs have the potential to produce adverse effects at muscarinic and nicotinic receptors resulting in an increase (vagolytic) or decrease (vagal) in heart rate. They can also, as with pancuronium, block release of norepinephrine and its reuptake at sympathetic nerve endings.[58] They may release histamine.[58] Abouleish,[1] Sparr,[106] Levy,[75] and Szenohradszky[107] all found a decrease in mean arterial pressure after rapacuronium, although none of the events required intervention, nor were the changes statistically significant. Whalley compared 20 patients given rocuronium 0.6 mg kg^{-1} with 21 patients given atracurium 0.5 mg kg^{-1} and found no differences between groups in the changes in heart rate and arterial pressure, in the 15 min after intubation and before skin incision, from control measurements obtained before induction of anaesthesia.[115] Shorten compared 15 elderly patients given rocuronium 0.9 mg kg^{-1} with 15 patients given vecuronium 0.12 mg kg^{-1} and found no significant change in heart rate, arterial pressure or plasma epinephrine, or norepinephrine concentrations in either group.[104]

Cisatracurium at doses of up to $8\times ED_{95}$ (0.4 mg kg^{-1}) has been shown to produce no significant changes in heart rate or mean arterial pressure in healthy patients.[76] In his study of cisatracurium by infusion in 40 critically ill patients, Newman found no significant haemodynamic changes in any of the patients.[92] Boyd studied two similar groups of critically ill patients who received cisatracurium or atracurium by bolus and infusion and no haemodynamic changes were reported in either group.[20] Ali[3] administered mivacurium 0.25 mg kg^{-1} to 91 patients, and Doenicke[34] administered mivacurium 0.15 mg kg^{-1} to 11 patients and mivacurium 0.21 mg kg^{-1} to 12 patients. Significant cardiovascular changes (transient tachycardia and hypotension) were only observed in Doenicke's study after the higher dose of mivacurium.

Studies of the cardiovascular properties of the tropinyl diesters have considered only the degree of vagal block produced. This is evaluated by studying the inhibition of the bradycardic response to peripheral stimulation of the cut right vagus nerve with 15–20 Hz supramaximal impulses delivered every 2 min. Gyermek found that all the tropinyl diesters studied produced vagal block in the rat.[49] The least potent compounds (which have the slowest onset of action and longest duration of effect), produced 70–90% vagal block, whereas the more potent tropinyl diesters (the most rapid onset of action and the most rapid offset) produced only 40% vagal block. Investigation of TAAC3 in anaesthetized cats also suggests that this tropinyl ester has the potential to produce changes in heart rate and arterial pressure.[4] The fact that as potency increases, the side-effect profile of these drugs becomes more favourable is encouraging, as it is these more potent agents which promise to be of most clinical benefit.

The cardiovascular side-effects of GW280430A have been investigated in dogs, cats, and human volunteers.[8 54 55 78] Heerdt measured heart rate, systemic and pulmonary artery pressures, left ventricular pressure, end-diastolic pressure, and cardiac index in beagles given increasing doses of GW280430A. Other than a transient decrease in arterial pressure at $25\times ED_{95}$, GW280430A did not alter any of the variables.[54 55] When Belmont examined the effect of GW280430A on the cardiovascular system of cats by measuring heart rate, arterial pressure and per cent vagal inhibition, he was able to give $10\times ED_{95}$ before producing a transient but significant decrease in arterial pressure and a rise in heart rate. Forty per cent vagal block was produced at $16\times ED_{95}$.[8] Lein has reported the effects of GW280430A in 16 male volunteers using doses up to $3\times ED_{95}$ and measuring maximal heart rate and arterial pressure changes in the 5 min following administration. She found that no volunteer had a maximal change in heart rate or arterial pressure of greater than 10% from baseline.[78]

Anaphylactoid reactions

The administration of a drug to a patient via the i.v. route can produce the release of vasoactive substances such as histamine, eicosanoids, and cytokines from inflammatory cells such as mast cells and basophils. The trigger for this release may be a true, immediate hypersensitivity response mediated through pre-sensitized mast cells with IgE antibody recognition.[114] However, certain drugs may directly affect inflammatory cells and the vascular system to produce adverse reactions that are often falsely labelled as allergic.[74] The clinical picture is an immediate systemic inflammatory response with hypotension, tachycardia, bronchospasm, and cutaneous flushing. The term anaphylactoid is used to describe this scenario, and when a genuine immune-mediated response can be demonstrated—anaphylactic.

Before the release of rapacuronium, it had been accepted that the aminosteroid neuromuscular blocking drugs cause less histamine release and are more cardiovascularly stable than the benzylisoquinolinium neuromuscular blocking drugs.[90] Levy,[75] McCourt,[83] Purdy,[98] Kahwaji,[61] and Abouleish[1] record skin erythema which settled without intervention in 1–2% of their patients after rapacuronium. Levy[75] studied plasma histamine levels after rapacuronium 1, 2, and 3 mg kg^{-1} and found a significant increase in histamine release at 1, 2, and 3 min post-dose in the 2 and 3 mg kg^{-1} groups; histamine levels were more than doubled in the high dose group.

Histamine release has been shown to be insignificant following doses of rocuronium up to 1.2 mg kg^{-1},[73] and Whalley studied 20 patients given rocuronium 0.6 mg kg^{-1} and found no episodes of skin erythema.[115] Anaphylactic reactions to rocuronium have now been described, however, in many cases confirmed by positive skin prick testing.[39 70 91 99] Laxenaire has reported almost 50 cases of anaphylaxis to rocuronium over 2 yr in France.[71] Rose has investigated 54 patients in Australia with suspected anaphylaxis to rocuronium and has described rocuronium as having a propensity to cause allergy intermediate between low risk (pancuronium and vecuronium) and high risk agents (e.g. succinycholine).[99] Neal has suggested that the incidence of anaphylaxis to rocuronium may be as great as 1:3000 in the UK and that careful monitoring of reactions to rocuronium is necessary.[91] When Levy studied the production of a weal and flare response to intradermal rocuronium and cisatracurium, he found that although both drugs were capable of producing this response (at concentrations of 10^{-4} M and above), light and electron microscopy of the skin biopsies revealed mild to moderate mast cell degranulation in the cisatracurium group only and normal mast cell morphology in the rocuronium group.[74] Despite these findings, several studies have recorded no significant increase in plasma histamine levels or the presence of skin erythema after administration of cisatracurium $8\times ED_{95}$.[35 36 76] Raised plasma histamine levels have been reported after mivacurium[34 70] as has cutaneous flushing.[3 34] Anaphylaxis after atracurium,[69 70] mivacurium,[6 70] and cisatracurium[25 70] have all been reported, however.

Summary

The pharmacodynamics and pharmacokinetics of the two most recent aminosteroid neuromuscular blocking drugs to become available, rapacuronium bromide (Org 9487) and rocuronium bromide are reviewed. Two new classes of drug with neuromuscular blocking properties, the bis-tetrahydroisoquinolinium chlorofumarates and the tropinyl diester derivatives are introduced. Comparisons between these drugs and mivacurium and cisatracurium are made.

Rapacuronium 1.5 mg kg^{-1} (ED_{95} 1 mg kg^{-1}), produces maximal neuromuscular block in 54 s. Time to recovery of the train-of-four ratio to 0.7 is achieved within 20 min after neostigmine 0.05 mg kg^{-1} given at 2 min. The plasma clearance of rapacuronium is 7–8 ml kg^{-1} min^{-1}.

Rapacuronium undergoes hepatic metabolism; no prolongation of effect has been reported after a single bolus or a short infusion in patients with hepatic or renal failure. Org 9488 is the 3-desacetyl metabolite of rapacuronium, which has neuromuscular blocking properties. Its much lower clearance (1.28 ml kg^{-1} min^{-1}) and plasma equilibration constant (0.105 min^{-1}) may limit the prolonged use of rapacuronium. Rocuronium given at $2\times ED_{95}$ produces maximal neuromuscular block in 1 min. Spontaneous recovery of the train-of-four ratio to 0.7 takes over 40 min. Rocuronium has a plasma clearance of 4 ml kg^{-1} min^{-1}. Its pharmacodynamics are altered in hepatic and renal disease. A number of anaphylactoid reactions to rocuronium have been reported recently.

The bis-tetrahydroisoquinolinium chlorofumarate GW280430A has an ED_{95} of 0.19 mg kg^{-1}. Given at three times this dose, onset of neuromuscular block occurs within 100 s; the duration of block is 8–9 min. Following a 2 h infusion, the recovery index does not seem to be increased. Early studies suggest that this drug has no adverse cardiovascular or respiratory side-effects.

The tropinyl diester derivative G-1-64 will produce 80–90% neuromuscular block in less than 2 min using $3\times ED_{80}$. Ninety per cent recovery of the first twitch of the train-of-four occurs after 5–7 min using one ED_{80}. A recovery index of less than 2 min has been reported in rats. All the tropinyl diesters appear to produce vagal block.

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BJA

SHORT COMMUNICATIONS

Thrombocytosis in intensive care

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We conducted a retrospective study of platelet count in 226 patients admitted for critical care over a 5-month period, to explore the incidence of thrombocytosis and its relation to admission category, duration of ICU stay and outcome. Our findings indicate that thrombocytosis is not rare in ICU patients. At least one platelet count greater than 450×10^9 litre^{-1} was found in 21.7% of patients and was associated with lower ICU mortality (P=0.003), lower hospital mortality (P=0.006), but longer duration of ICU stay (P<0.0001). Thrombocytosis may serve as an independent predictor of favourable outcome in ICU patients.

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Keywords: intensive care, mortality; blood, platelets, thrombocytosis

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Marked variations of platelet count between patients and in the same patient over time are common in intensive care unit (ICU) patients. The causes of thrombocytopenia have been extensively reviewed[1] and thrombocytopenia has been shown to be predictive of an adverse outcome.[2] We are unaware of any previous literature specific to the prognostic value of thrombocytosis in intensive care medicine.

The purpose of this study was to explore the incidence of thrombocytosis and its relation to duration of ICU stay and outcome. Thrombocytosis may serve as an additional variable in prediction of outcome in ICU patients.

Methods and results

All patients admitted to the general ICU (GICU) and trauma ICU (TICU) of the North Staffordshire Hospital, Stoke-on-Trent, UK from January 1 to May 31, 2000 were included in this retrospective study. Data related to age, sex, duration of ICU stay, outcome, admission category, APACHE II score, and predicted mortality were obtained from HISS (Hospital Information Support System) and Acubase – ICNARC (Intensive Care National Audit Research Centre) databases. Duration of stay was rounded to the nearest whole day, with any duration of stay less than 24 h counted as 1 whole day. If the patient was admitted more than once, or transferred from one unit to another, then it was considered as a single admission. The initial platelet count (for the first admission) and the highest and the lowest platelet counts during the whole duration of ICU stay were recorded. On the basis of these results, patients were retrospectively divided into three groups: those with a platelet count less than 150×10^9 litre^{-1} on at least one occasion; those whose platelet count remained between 150 and 450×10^9 litre^{-1} throughout; and those whose platelet count exceeded 450×10^9 litre^{-1} on any occasion. The day of ICU stay on which the latter occurred was also recorded. Unless contraindicated, thromboprophylaxis with graduated compression stockings and subcutaneous heparin was used in all patients.

Continuous variables are expressed as number and percentage of the group from which they were obtained, or median and interquartile range. Continuous variables were analysed using the Kruskal–Wallis test. The Mann–Whitney test was used to compare duration of ICU stay between patients with early and late onset of thrombocytosis. Discrete variables were analysed using chi-squared tests. Statistical analyses were performed using StatView® version 4.02 for Macintosh and a P value of <0.05 was considered significant.

A total of 231 patients were admitted during the study period: to the GICU, 104 and to the TICU, 127. Four patients with no documented platelet count and one patient transferred to an ICU in another hospital were excluded. The platelet count of 226 patients and admission category, predicted mortality, ICU outcome and hospital outcome were analysed (Table 1). Thrombocytosis, defined as a platelet count of greater than 450×10^9 litre^{-1} on at least one occasion, was observed in 49 patients (21.7%). The median onset of thrombocytosis was 7 (1–11) days after ICU

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Table 1 Patient characteristics in the three groups. Values are number (percentage) of occurrences or median (interquartile range). Between group comparisons were analysed using the Kruskal–Wallis test† for continuous variables, and the chi-squared test‡ for discrete variables. A three by three chi-squared test was performed to study the distribution of medical surgical and trauma patients between the three groups (P=0.061)

	Total	**Platelet count×10^9 litre^{-1}**			***P* value**
		<150	**150–450**	**>450**	
Number (%)	226	67 (29.6%)	110 (48.7%)	49 (21.7%)	
Age (yr)	55 (37–67)	58 (40–67)	51.5 (32–66)	54 (38.5–67)	0.348†
Males	132 (58.4%)	34 (50.8%)	70 (63.6%)	28 (57.1%)	0.236‡
Admission category					0.061‡
Medical	67 (29.6%)	16 (23.9%)	39 (35.4%)	12 (24.5%)	
Surgical	70 (31%)	29 (43.3%)	28 (25.5%)	13 (26.5%)	
Trauma and neurosurgery	89 (39.4%)	22 (32.8%)	43 (39.1%)	24 (49%)	
Predicted mortality (%; n=165)	23 (11–39)	25 (9–42)	19.5 (10–43)	23 (14–37)	0.939†
ICU mortality	45 (19.9%)	21 (31.3%)	21 (19.1%)	3 (6.1%)	0.003‡
Hospital mortality	59 (26.1%)	27 (40.3%)	24 (21.8%)	8 (16.3%)	0.005‡
ICU stay (days)	2 (1–9)	2 (1–8)	1 (1–3)	13 (4–24)	<0.0001†

admission, although 39% of patients either had thrombocytosis at ICU admission or developed this within 4 days. Patients with at least one platelet count higher than 450×10^9 litre^{-1} had lower ICU and hospital mortality but a longer duration of ICU stay, despite similar predicted mortality (Table 1). The median (range) duration of ICU stay (18.5, 13–33 days) was significantly longer in patients who developed thrombocytosis after 4 or more days in the ICU compared with those with an earlier thrombocytosis (3, 1–6 days; P<0.0001), although the mortality of these two subgroups did not differ significantly.

Comment

Thrombocytosis is common in ICU patients. Among our patients, 21.7% had at least one platelet count greater than 450×10^9 litre^{-1}. Thrombocytosis can be primary or reactive to a variety of causes. Extreme thrombocytosis should not be considered a rare event in a general, acute care hospital population, and usually represents a reactive phenomenon.[3] Reactive thrombocytosis has been reported to occur as a response to various conditions, such as post-splenectomy and in haematopoietic disorders, major trauma and surgery, neoplasms, and inflammation.[4] Increases in platelet count have previously been shown to be associated with improved survival in ICU,[5] although none of those patients had platelet counts in excess of 450×10^9 litre^{-1}. Indeed, most of the deaths in that series[5] occurred in patients with thrombocytopenia, which is well recognized to be associated with poor survival.[2]

We are unaware of any previous literature describing the association between a high platelet count and outcome in critically ill patients. We found that a platelet count higher than 450×10^9 litre^{-1} on at least one occasion during the ICU stay was associated with lower ICU and hospital mortality. This was equally true for patients presenting to ICU with an established thrombocytosis and for those developing it later. Indeed, a small cohort of patients (n=14) developed a thrombocytosis after presenting with an initial platelet count of less than 150×10^9 litre^{-1}. These patients were included with the thrombocytosis group, but even when analysed separately, they were still associated with a more favourable outcome compared with patients without a thrombocytosis. As thrombocytopenia is associated with poor outcome,[2] we compared our patients with thrombocytosis against patients with thrombocytopenia as well as those with a normal platelet count throughout; outcome was more favourable compared with either group. Overall, thrombocytosis was associated with a prolonged ICU stay, although this was far less marked in patients presenting to ICU with thrombocytosis or developing it at an early stage.

Despite these findings, this study has some limitations. It is a retrospective study. Some patients were not on the ICU for sufficient time for all data required to calculate predicted mortality to be collected. However, the distribution of these patients did not differ between the three groups defined by platelet counts. Being the major trauma receiving hospital in the region, the proportion of patients admitted with multiple trauma including head injury requiring neurosurgery is high, which is the reason for grouping these categories of patient together in our study. Thrombocytosis was more common in this patient category.

In conclusion, thrombocytosis is a common finding in ICU. It appears to be associated with lower ICU and hospital mortality but longer duration of ICU stay. It may serve as an additional variable in predicting outcome in ICU patients. A large prospective study is required to confirm these findings.

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Preoxygenation: a comparison of three different breathing systems

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An end-tidal expiratory oxygen concentration (FE'_{O_2}) greater than 0.90 is considered to be adequate for preoxygenation. This is generally achieved using a face mask, but this can be unsatisfactory in some patients. We compared preoxygenation in 30 healthy volunteers using a face mask, the NasOral system, which is a novel preoxygenation device, and a mouthpiece with a nose-clip. We measured the maximal FE'_{O_2}, the FE'_{O_2} after 2 min and the time to reach maximal FE'_{O_2} and recorded the subjective judgement of the volunteers. The maximal FE'_{O_2} with face mask and mouthpiece was significantly greater than with the modified NasOral system ($P<0.05$ and $P<0.01$). With the former devices, a FE'_{O_2} of 0.90 was achieved in 73% of the volunteers *vs* 46% with the modified NasOral system. Using the mouthpiece, the FE'_{O_2} after 2 min was significantly higher than using the face mask ($P<0.01$) or the modified NasOral system ($P<0.01$). The time to maximal FE'_{O_2} was significantly shorter using the modified NasOral system than with the face mask or mouthpiece ($P<0.001$ and $P=0.0001$). The volunteers gave more positive ratings to the face mask and mouthpiece than to the modified NasOral system ($P<0.001$ and $P<0.01$). We conclude that the use of a mouthpiece can improve preoxygenation in some patients. The results obtained with the modified NasOral system do not justify its introduction into clinical practice.

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Preoxygenation is a standard procedure to prevent arterial desaturation during the induction of general anaesthesia.[1] It is considered to be adequate if end-tidal expiratory oxygen concentration FE'_{O_2} is greater than 0.90.[2–4] This is most often achieved by 1.5–3 min of tidal volume breathing with 100% oxygen via a face mask.[4 5] The use of a mouthpiece with a nose-clip has been shown to provide a similar FE'_{O_2}.[3 6] Recently, a novel device for preoxygenation, the NasOral system, has been introduced.[7 8] Inspiration with this system is from a nasal mask equipped with a one-way valve and a reservoir bag that ensures a steady, unidirectional gas flow. The patient exhales via a sealed mouthpiece, which is also fitted with a one-way valve.[9] The expense of this system and the need for different tubing has prevented further evaluation. Therefore, we fitted the valves in the inspiratory and expiratory branches to allow re-use of the whole tubing system, including the reservoir bag (Fig. 1).

Materials and methods

We compared preoxygenation with tidal volume breathing using a standard face mask, a mouthpiece with a nose-clip and the modified NasOral system using the following variables: (1) the maximal FE'_{O_2} and the ability to obtain an

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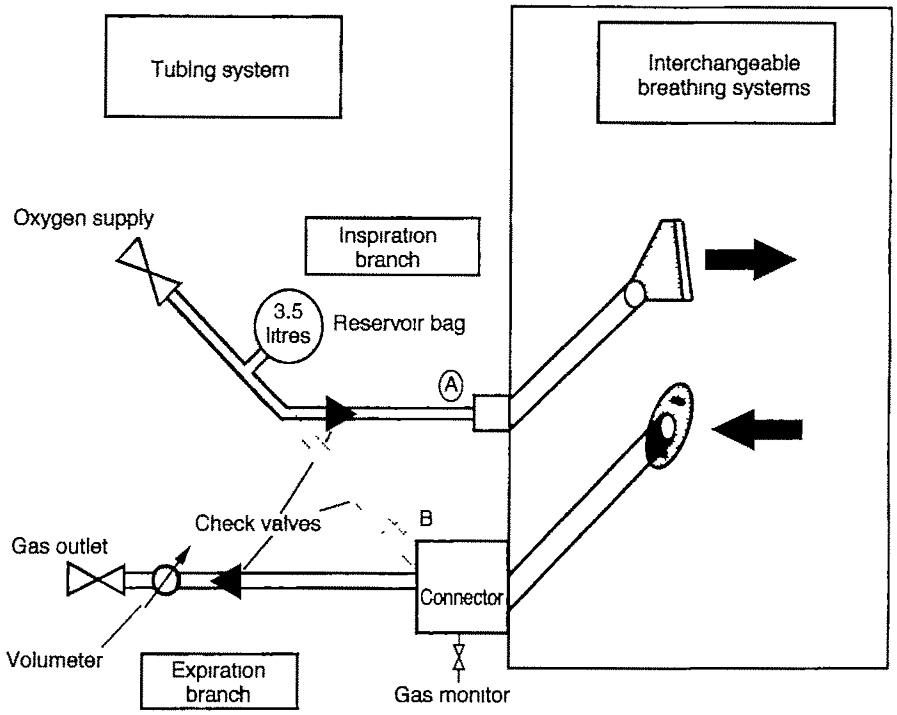

Fig 1 On the left, the tubing system fitted with a 3.5 litre reservoir bag is shown. The valves in the inspiratory and expiratory branches create a unidirectional gas flow. Preoxygenation with the NasOral system was performed as shown with the inspiratory branch in position A. Using the face mask or mouthpiece, the tubing was connected as indicated in position B. The connector consisted of a standard Y-piece and a filter and had a volume of about 30 ml. By connecting a mouthpiece with a nose-clip, a face mask and a NasOral system (as shown on the right) to this tubing system, the efficacy of the three devices was compared

$F\mathrm{E}'_{\mathrm{O_2}}$ of 0.90; (2) the $F\mathrm{E}'_{\mathrm{O_2}}$ after preoxygenation for 2 min; (3) the subjective judgement of the volunteers on the devices.

The study was approved by the ethics committee of the Free University of Berlin. Thirty healthy, non-smoking volunteers whose age ranged from 22 to 70 yr (median 44.5 yr) were included after pulmonary function testing to exclude respiratory disease. All tests were performed using a standardized breathing system (Fig. 1). To supply 100% oxygen, the inhalation limb of a Sulla 808 respirator (Drägerwerk, Lübeck, Germany) was used. The concentrations of oxygen and carbon dioxide in every breath were measured using a gas monitor (M 1026 A; Hewlett-Packard, Palo Alto, CA, USA) that was connected to the respiration system via a sampling tube (HP 13901A; Hewlett-Packard). The gas monitor was calibrated before the experiments using a standardized gas sample (HP 13906B; Hewlett-Packard). The expiratory minute volume was measured by a calibrated volumeter (Datex-Ohmeda, Helsinki, Finland).

A standard respiratory mask (Rüsch Hospital Vertriebs, Vertriebs GmbH, Boblingen, Germany), a mouthpiece with a nose-clip (preOX-RS, Schwalbach, Germany) and a one-way NasOral-system (preOX-RS) were connected to the tubing system (Fig. 1). Because of the modifications, some mixing between the inspiratory and expiratory air occurred at the connector when the face mask and the mouthpiece were used. The connector consisted of a standard Y-piece and a small filter. The volume between the junctions of the Y-piece and the content of the filter was about 30 ml. Testing for leaks was done by connecting the gas outlet to the expiration branch of the respirator and testing for leakage according to the manufacturer's instructions. Inspiratory oxygen flow was adjusted to about 8 litre min^{-1} to keep the reservoir bag half-filled but not distended. The trials were performed in different sequences. For the purpose of the analysis, six volunteers were allocated to one of five age groups. The volunteers were studied supine with 20° head elevation. The studies were done by one examiner in a standard way. Every trial was started with room air to measure the baseline $F\mathrm{E}'_{\mathrm{O_2}}$. Hyperventilation (defined as a $F\mathrm{E}'_{\mathrm{CO_2}}$ of less than 32 mmHg) was ruled out by capnometry. After four tidal volume breaths, the system was switched to 100% oxygen. Recording was continued until there was no further change in the $F\mathrm{E}'_{\mathrm{O_2}}$ of three consecutive breaths, which was defined as the maximal $F\mathrm{E}'_{\mathrm{O_2}}$. Between the tests, the volunteers breathed room air for a minimum of 10 min until the $F\mathrm{E}'_{\mathrm{O_2}}$ had returned to the basal value. After completion of the test series, the volunteers were asked to score the devices for comfort, a feeling of adequate gas supply, and anxiety using, a visual analogue scale (VAS).

Statistical analysis was performed using SPSS 9.0 for Microsoft Windows. For comparisons, the Wilcoxon test, rank correlation analysis according to Spearman, the χ^2 test and Fisher's exact test were used. Data are given as mean (SD).

Results

Expiratory minute volume

The expiratory minute volume of the volunteers was significantly less with the face mask [9.6 (1.1) litres] and the mouthpiece [9.5 (1.2) litres] than with the NasOral system [10.8 (1.6) litres] (both $P<0.001$). There was no significant difference between face mask and mouthpiece.

$F\text{E}'_{\text{O}_2}$

Using the face mask, the maximal $F\text{E}'_{\text{O}_2}$ was significantly higher [91.0 (2.9)%; maximum 95.0%, minimum 82.4%] than with the modified NasOral system [87.3 (8.4)%; maximum 96.5%, minimum 54.5%] ($P<0.05$). Preoxygenation with the mouthpiece gave a greater maximal $F\text{E}'_{\text{O}_2}$ [92.1 (2.6)%; maximum 96.0%, minimum 84.0%] than the face mask ($P<0.05$) and modified NasOral system ($P<0.01$). A $F\text{E}'_{\text{O}_2}$ of 0.90 was reached by 73% (22 of 30) of the volunteers with the face mask or mouthpiece. Only 46% (14 of 30) of the volunteers were able to reach a $F\text{E}'_{\text{O}_2}$ of 0.90 using the modified NasOral system. This did not vary according to the age of the volunteers. There was no statistically significant correlation between the $F\text{E}'_{\text{O}_2}$ that any volunteer obtained with different preoxygenation devices.

Using the mouthpiece, the $F\text{E}'_{\text{O}_2}$ after 2 min was significantly greater than using the face mask [91.0 (3.0)%; maximum 96.0%, minimum 84.5% *vs* 89.0 (4.2)%; maximum 94.0%, minimum 76.0%; $P<0.01$] or the modified NasOral system [86.6 (8.6)%; maximum 95.5%, minimum 52.5%; $P<0.01$]. There was no statistically significant difference between face mask and modified NasOral system.

The time needed to reach the maximal $F\text{E}'_{\text{O}_2}$ was significantly less using the NasOral system [100 (30) s; maximum 171 s, minimum 34 s] than using the face mask [131 (31) s; maximum 180 s, minimum 67 s] ($P<0.001$) or the mouthpiece [132 (28) s; maximum 192 s, minimum 88 s] ($P=0.0001$). There was no significant difference between face mask and mouthpiece.

VAS ratings

There was no significant difference between the VAS ratings of face mask and mouthpiece [66 (23.0) *vs* 68 (23.5)%]. Both had significantly better ratings than the modified NasOral system [42 (25)%] (both $P<0.01$).

Comment

Our finding that, using a face mask, a $F\text{E}'_{\text{O}_2}$ of 0.90 can only be reached in about 75% of persons confirms previous studies.[10] Poor patient cooperation, anxiety, the shape of the patient's face, a beard, facial burns, trauma and obesity can impede the face mask seal. A good face mask seal is necessary for adequate preoxygenation [11] Because many of the factors above are also risk factors for difficult tracheal intubation, good preoxygenation is important for safety during induction of anaesthesia.[1] $F\text{E}'_{\text{O}_2}$ measurement has become common practice in most centres. Therefore, patients who cannot be preoxygenated sufficiently with a face mask can be identified before anaesthesia induction. In our study, the results of preoxygenation with one breathing system was not significantly correlated to the results with the other devices. A patient who cannot be adequately preoxygenated with a face mask may therefore be preoxygenated sufficiently with another breathing system.

Our results indicate that a mouthpiece with a nose-clip can be an alternative for preoxygenation. The disadvantage of preoxygenation using a mouthpiece, however, is the difficulty of ventilating the patient after induction of anaesthesia. Furthermore, infants and about 7% of adults are reported to have difficulty breathing by the oral route. This appears to be more common in the elderly.[12]

The time to reach the maximal $F\text{E}'_{\text{O}_2}$ was significantly less with the modified NasOral system, which is partly explained by the higher expiratory minute volume using this system. However, fewer volunteers reached an $F\text{E}'_{\text{O}_2}$ of 0.90 and the mean $F\text{E}'_{\text{O}_2}$ was less, which are significant disadvantages. These results are surprising, because preoxygenation with the NasOral system has the advantage in principle that no expiratory air re-enters the inspiration branch. We did not observe significant leakage of the nasal mask included with the NasOral system. The probable reason for the poor results is the special breathing technique necessary with the modified NasOral system. Difficulties with this technique were reported by many of the volunteers and could explain the limited acceptability of this system. The breathing technique with the modified system is not different from that with a standard NasOral system. The compliance of emotionally distressed patients would certainly be much worse than in the quiet setting of a controlled study. Therefore, our results do not support the introduction of this system into clinical practice.

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BJA

CASE REPORTS

Epidural haematoma after dural puncture in a parturient with neurofibromatosis

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A case of epidural analgesia in a parturient with neurofibromatosis (von Recklinghausen's disease) complicated by dural puncture and epidural haematoma is described and the management of the case is discussed. The case emphasizes the need for antenatal assessment of parturients with neurofibromatosis in order that the necessary investigations can be arranged and informed consent for analgesia and anaesthesia can be obtained.

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Neurofibromatosis is an autosomal dominant condition with variable expressivity and an incidence of 1 in 3000 live births. The classical disease is characterized by multiple neurofibromata of peripheral nerves and cutaneous pigmentation patches (café au lait spots). In the only previous case report of regional analgesia in neurofibromatosis, the condition was identified, the parturient was investigated antenatally and the clinical course was uncomplicated.[1] However, when the condition is not recognized the parturient may be exposed to considerable risk from attempts to provide regional analgesia.

Case report

A 41-yr-old nulliparous woman at 39 weeks gestation and in established labour requested epidural analgesia. She had booked late (at 20 weeks) and her antenatal care was unremarkable. She gave no medical history of note, but on examination by the anaesthetic trainee multiple pedunculated skin lesions were noted over her trunk, face and limbs (Fig. 1). She said she had been diagnosed with a skin condition, the name of which she could not recall. However, she was told it was of little significance. She gave no family history and her medical notes were unavailable. Her cervix was 4 cm dilated.

After routine verbal consent, an epidural catheter was sited uneventfully at L5/S1 level, avoiding passage through any of the skin lesions. An effective epidural block was obtained with a low-dose bupivacaine/fentanyl solution. Two boluses were given over the next 3 h, but then analgesia became ineffective as the catheter had migrated out of the epidural space and so was removed. Vaginal examination revealed an 8 cm dilated cervix, and at maternal request attempts were made to resite the epidural catheter. On location of the epidural space at the L3/4 level, the catheter fed into an epidural vein. Blood continued to be aspirated after catheter withdrawal so the catheter was removed. Then at the L4/5 level, inadvertent Tuohy needle dural puncture occurred so senior assistance was requested.

The medical notes had been obtained and revealed a diagnosis of neurofibromatosis. After review of the case and in the light of the complications already experienced by the patient, a combined spinal–epidural (CSE) was performed uneventfully by the consultant anaesthetist at the L2/3 level. This gave rapid relief and was effective with epidural boluses. After a further 6 h, the patient's cervix was fully dilated but the fetal head was high. The obstetric team,

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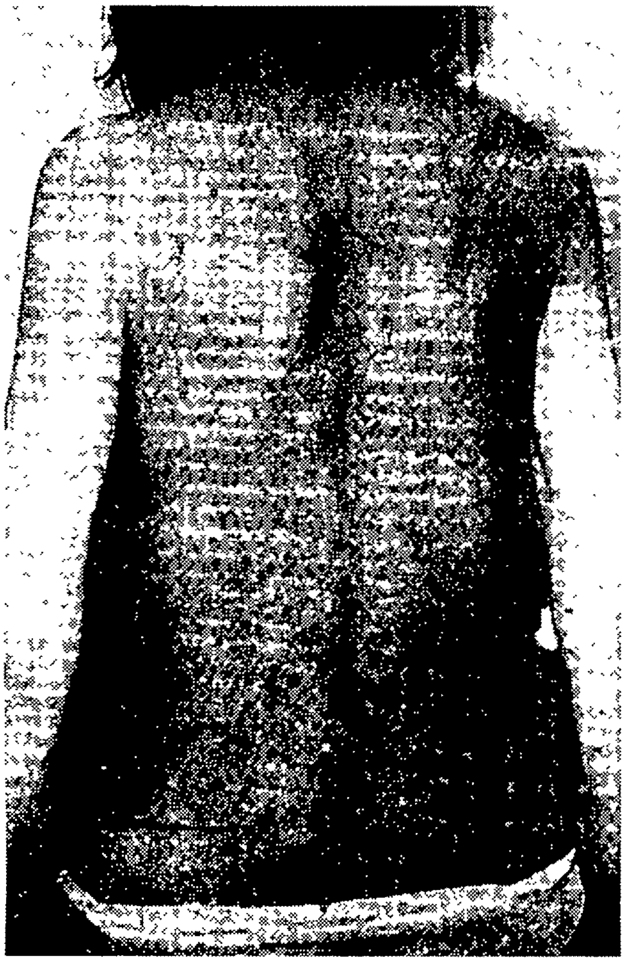

Fig 1 View of the parturient's back, demonstrating multiple pedunculated skin neurofibromata.

informed of the dural puncture, allowed limited pushing in the second stage. The fetal head remained high, so after a trial of forceps in the operating theatre, a Caesarean section was performed uneventfully under epidural anaesthesia. The second stage was prolonged to 3.5 h as the obstetric team were occupied with other cases.

Review the following morning was unremarkable, the patient having mobilized with no headache or back pain. She was given diclofenac for postoperative pain, and did not receive heparin thromboprophylaxis. On the second postoperative day, she developed urinary incontinence and was recatheterized. Neurological examination revealed upgoing plantar reflexes bilaterally, but no other abnormal neurology. In particular, perianal sensation and anal sphincter tone were normal. An urgent magnetic resonance imaging (MRI) scan was performed, which showed an epidural haematoma at the L4/5 level. The haematoma was not impinging sufficiently on the dural sac to cause cauda equina compression. Neurosurgical review confirmed that no intervention was indicated.

The patient was reassured, and her urinary incontinence resolved by the third postoperative day. Follow-up cerebral and spinal MRI scan after 4 weeks revealed resolution of the epidural haematoma and no neurofibromata. The patient was advised that if she should become pregnant again, early obstetric and anaesthetic consultation should occur.

Discussion

The clinical presentations of neurofibromatosis and some anaesthetic implications have been reviewed recently.[2] While this patient had no neurological symptoms, spinal tumours have been identified in 40% of patients with asymptomatic classical neurofibromatosis.[3] The majority of tumours arise laterally at the intervertebral foramen but are at risk of direct trauma from an epidural needle if they extend towards the midline.[4]

It has been suggested that a potential complication after dural puncture could be rapid decompression below a spinal or intracranial tumour, causing spinal cord injury or even death, particularly in the presence of raised intracranial pressure.[1 2] MRI or computed tomography scanning of the brain and spinal cord is recommended late in pregnancy, as tumours may grow significantly during gestation.[5]

This condition, in common with many neurological conditions, may be viewed as a relative contraindication to regional analgesia. A risk–benefit analysis should be made, thorough neurological examination recorded and detailed informed consent gained before proceeding. Alternative methods of pain relief, including nitrous oxide/oxygen and systemic opiate analgesia, should be considered.

This patient ultimately required Caesarean section for failure to progress, and it is unlikely that epidural analgesia influenced this outcome.[6] Alternative anaesthesia for operative delivery would have included general anaesthesia. While neurofibromatosis has been associated with abnormal responses to neuromuscular blocking drugs, this has recently been contested.[7 8] Airway problems have also been described,[9] but this parturient had a clinically normal cervical spine, unremarkable airway assessment and no history of general anaesthetic complications.

This parturient booked late but otherwise had routine antenatal care. We were unaware of her diagnosis until her medical notes were obtained, by which time less than fully informed consent for epidural analgesia had been taken, and the bloody tap and dural puncture had already been made. Further clinical examination revealed several café au lait spots and the clinical diagnosis was not in doubt.

Consideration was given to passing an intrathecal catheter via the Tuohy needle after dural puncture, but at the time this was against department practice. The CSE technique was performed to give rapid relief to the parturient, who was increasingly distressed. Any additional leak from a 27 gauge Whitacre spinal needle puncture was not considered significant in comparison with the 16 gauge Tuohy needle puncture. Recent reports of conus damage from spinal anaesthesia administered at levels above Tuffier's line suggest that CSE at the L2/3 level exposes the parturient to risk from this complication, however, and should be avoided.[10]

Parturients with pre-existing neurological conditions require neurological examination after regional blockade. The upgoing plantar reflexes elicited and bladder dysfunction led to urgent MRI investigation. No cause for these findings was identified but an epidural haematoma was found at the L4/5 level. While clinical identification of spinal levels may be inaccurate,[11] this was thought to be the level of the dural puncture.

As many as 80–85% of parturients with dural puncture experience postdural puncture headache[12] [13] but our patient remained headache-free, perhaps because of the 'blood patch' effect of the epidural haematoma. Previous retrospective review of one unit's dural punctures showed no protective effect of bloody tap in relation to the development of postdural puncture headache.[14] Other work suggests that bloody tap is usually associated with only a small volume of epidural blood, not adhering to the thecal sac.[15] In our case, impingement on the dural sac by the haematoma was seen at the level of the dural puncture, and hence an 'auto-blood patch' effect may have occurred.

The upgoing plantar reflexes remain unexplained and, because this parturient presented to the anaesthetist in labour, a full baseline neurological examination was not performed. This again emphasizes the need for good communication between obstetric and anaesthetic staff so that these patients can be identified, assessed and investigated before the onset of labour.

Bladder dysfunction after extended labour is well recognized. After a long second stage with a high fetal head, lumbosacral plexus neuropraxia seems a possible cause in this case as recovery was rapid. Maternal obstetric palsies are commonly attributed to regional techniques[16] and, as Bromage has reiterated, it is vital that practising anaesthetists become skilled and active in bedside neurological diagnosis.[17]

While all the problems experienced by this parturient in association with our regional anaesthetic techniques would have occurred in the absence of neurofibromatosis, our diagnosis of her condition, albeit late, heightened our awareness of potential problems. This re-emphasizes the fact that thorough assessment of parturients with neurological conditions antenatally is vital so that analgesia and anaesthesia can be planned and, ideally, informed consent can be gained in advance. Experience of obstetrical anaesthesia assessment clinics suggests they may facilitate this,[18] and in such a way adverse outcomes for parturients may be prevented.

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Epidural analgesia in a child with sickle cell disease complicated by acute abdominal pain and priapism

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We describe a case of a 9-yr-old child with sickle cell disease complicated by abdominal vaso-occlusive crisis and priapism. Both complications were successfully treated with a combination of epidural local anesthetics and morphine.

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Keywords: blood, sickle cell disease; complications, priapism; anaesthetic techniques, epidural

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Vaso-occlusive crises are the most frequent and debilitating problems encountered by patients with sickle cell disease. They are because of recurrent vaso-occlusive phenomena, their incidence ranges between 0.8 and 1 episode per patient per year [1] [2] They are responsible for severe organ dysfunction.[2] Current management is essentially supportive and conservative, for example analgesia, hydration, oxygenation, transfusion, and blood exchange.

The reported incidence of severe priapism in children with sickle cell disease is 2–5%.[3] Priapism is a persistent painful erection usually unrelated to sexual activity and, if untreated, will result in impotence. Emergency medical treatment is recommended and, in case of failure, surgical methods are indicated. We present a case in which a child with severe abdominal vaso-occlusive crisis and priapism was successfully treated with a combination of epidural local anesthetics and morphine.

Case report

A 9-yr-old boy, 35 kg, with a sickle cell disease was hospitalized because of severe abdominal pain (8/10 on a visual analogue score (VAS)). Initial treatment consisted of hydration, propacetamol (120 mg kg^{-1} day^{-1}), nalbuphine (200 µg kg^{-1}) and oxygen (2 litre min^{-1}). The patient was transferred 24 h later to the intensive care unit because of worsening of abdominal pain (VAS 10/10). The patient had normal bowel sounds and no rebound tenderness. Radiological and laboratory data provided no indication for a laparotomy. A continuous morphine infusion (20 µg kg^{-1} h^{-1}), complicated by vomiting and sedation (De Koch sedation score 2),[4] was then started, followed by a partial exchange transfusion to reduce the concentration of sickle cell haemoglobin from 63 to 36%. Within 2 h, the abdominal sympróms improved (VAS 5/10). However, the patient developed an episode of priapism 9 h later. Because of the occurrence of this complication, in spite of conventional management (hydration, oxygenation, and exchange transfusion), a decision was made to place a lumbar epidural catheter. No further sedation was necessary of the effects of the continuous morphine infusion (sedation score 2) A 18G Tuohy needle was inserted at L4–L5 level, the epidural space being identified by loss of resistance to saline, and the epidural catheter was inserted without complications. The patient received a 17-ml bolus of 0.25% bupivacaine with epinephrine 1/200 000 (Astra-Zeneca, Rueil-Malmaison, France) followed by a continuous infusion of 0 1% bupivacaine and morphine (40 µg ml^{-1}) at 12 ml h^{-1}. The i.v. infusion of morphine was stopped. Priapism resolved within 15 min after the initial bolus and abdominal pain improved (VAS 3/10) The patient developed urinary retention, requiring bladder catheterization and motor block of the lower extremities (grade 1 on the Bromage score).[5] The epidural catheter was removed 48 h later. The patient did not require supplemental analgesia and did not have further episodes of pain or priapism during the course of his hospital stay.

Discussion

We have described the use of epidural analgesia for the treatment of a severe abdominal vaso-occlusive crisis and priapism in a child with sickle cell disease. Epidural analgesia with local anesthetics has been shown to effectively treat the abdominal pain of a sickle cell vaso-occlusive crisis unresponsive to conventional pain management[6] and

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to resolve cases of priapism because of neoplasm, spinal cord injury and trauma[7] as well as idiopathic cases.[8] However, there are no data in the literature on the effect of epidural analgesia on priapism secondary to vaso-occlusive crisis.

There are two types of priapism: high and low flow. High flow priapism results from an increased arterial inflow into the cavernosal sinusoids and is generally post-traumatic or secondary to central neuraxis block. Low flow or ischaemic priapism is because of decreased penile venous outflow and is secondary to sickle cell disease tumour infiltrate[9] or anti-hypertensive medications.[10] It also can be idiopathic.[11] In patients with sickle cell disease, onset is often in the early morning and associated with long nocturnal erections. The underlying mechanism of priapism is an obstruction of venous outflow. Blood stasis with relative deoxygenation and acidosis favours sickling of erythrocytes.[12] In this case report, epidural anesthesia resolved promptly the episode of priapism, which was most likely of the low flow type.

The immediate resolution of this episode of priapism seems to contradict previous reports where patients experienced episodes of priapism after spinal and epidural anesthesia.[13 15] While the reasons for these episodes of priapism after central blocks are not well understood, they seem to be secondary to an increased parasympathetic tone followed by dilatation of penile arteries,[7] a situation that creates a condition of high flow. The rapid resolution observed in our patient suggests that, in patients with a vaso-occlusive crisis and a condition of low flow, epidural anesthesia might help by restoring normal venous outflow. Therefore, this technique should be used only in low flow types of priapism, because it may worsen cases of high flow priapism. Further studies are needed to determine whether epidural anesthesia has simply an analgesic effect in patients with vaso-occlusive crisis or if it plays a role in terminating the vaso-occlusive crisis itself by inducing a venodilatation. This case report shows that epidural anaesthesia can be a valid alternative to surgical procedures in cases of priapism resistant to conventional management and in patients with early recurrences.[12 16]

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British Journal of Anaesthesia **87** (6): 937–8 (2001)

Successful defibrillation in the prone position

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Early defibrillation provides the greatest chance of survival after ventricular fibrillation. Conventional cardiopulmonary resuscitation and defibrillation requires the patient to be in the supine position. Electrical treatment of arrhythmias such as atrial fibrillation by means of a defibrillator back paddle in patients receiving prone ventilation in intensive care has been described. We report a case in which electrical defibrillation was successfully performed in the prone position in a patient undergoing complex spinal surgery. We suggest that, if defibrillation were required in ventilated patients positioned prone, defibrillation should be attempted in the prone position, as turning the patient supine would consume valuable minutes and reduce the chances of successful defibrillation.

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Keywords: heart, ventricular fibrillation; heart, defibrillation, early; position, prone; surgery, spinal

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We describe a case of successful treatment of ventricular fibrillation by electrical defibrillation in a patient undergoing complex spinal surgery in the prone position.

Case report

A 39-yr-old female presented for palliative debulking of metastatic tumour of the third thoracic vertebral body and internal fixation of the thoracic spine to prevent spinal cord compression. The primary tumour was a squamous cell carcinoma of the lung, which had been treated with chemotherapy and radiotherapy. The patient was otherwise in good health and on the following medication: dexamethasone, low molecular weight heparin, lansoprazole, naproxen, fentanyl patches and hydromorphone. Preoperative haematological and biochemical investigations revealed no abnormalities (the serum potassium concentration measured 36 h preoperatively was 4.8 mmol litre^{-1}).

Prior to induction of anaesthesia, a few isolated unifocal ventricular ectopic beats were noted on the ECG monitor; the blood pressure was not affected. General anaesthesia was induced with midazolam, fentanyl and propofol. Tracheal intubation was facilitated by vecuronium and anaesthesia was maintained with oxygen/nitrous oxide and infusions of remifentanil and propofol. After induction of anaesthesia, runs of unifocal ventricular ectopic beats were noted, lasting for 2–3 s and occurring every 2–3 min; these had no effect on the arterial blood pressure trace.

In the operating theatre, the patient was turned prone onto a Montreal mattress and the head fixed in position on a Mayfield head-holder (Ohio Medical Instruments, Cincinnati, USA) with pins inserted into the skull. After commencement of surgery the runs of ventricular tachycardia continued to occur, but were well tolerated. The serum potassium concentration was measured and found to be 3.6 mmol litre^{-1}. An infusion of potassium chloride 20 mmol was commenced *via* the femoral venous line. Twenty minutes after the potassium infusion was started, the arterial blood pressure trace was suddenly lost and the ECG monitor showed ventricular fibrillation. This persisted despite the administration of a sharp thump to the back of the chest, and compressions were commenced on the back of the chest. At this stage there was a large open surgical wound in the upper back although no metalwork had as yet been inserted The infusion of potassium chloride was stopped (10 mmol had been given), anaesthetic agents were discontinued and the lungs ventilated with 100% oxygen. A defibrillator (Lifepack 6, PhysioControl, Redmond, USA) was brought to the scene, and two standard electrode gel pads (3M) placed on the back of the chest on either side of the surgical wound, one low down on the left side just posterior to the

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mid-axillary line, and the other just inferior to the right scapula. A single shock of 200 J was administered and was followed by the return of sinus rhythm. As the patient remained haemodynamically stable after this, it was decided to continue with the surgery. The serum potassium concentration was measured and found to be 7.2 mmol litre^{-1}. A second blood sample was taken 7 min later to ensure that the elevated serum potassium measurement was not due to an artefact from haemolysis or inappropriate blood sampling and was found to be 6.1 mmol litre^{-1}. The ampoules of potassium chloride were checked to ensure that no errors in the dosage of potassium chloride administered had occurred. Five millimoles of calcium gluconate and an infusion of amiodarone were started. After 30 min the serum potassium concentration was 4.1 mmol litre^{-1}. The operation was completed uneventfully, with no further arrhythmias occurring. At the conclusion of surgery, the trachea was extubated and the patient was observed for the next 24 h in the intensive care unit (ICU). She remained stable although occasional ventricular ectopic beats continued to occur.

A 12-lead electrocardiogram revealed no abnormalities. However, on direct questioning the patient admitted to a 10-year history of palpitations, without accompanying symptoms, which had never been investigated or treated. She was reviewed by a cardiologist who recommended that amiodarone should be continued, and she was discharged from hospital a week later after an uneventful postoperative course.

Discussion

Electrical treatment is the only effective treatment for ventricular fibrillation, and *early* defibrillation provides the greatest chance of survival.[1]

The European Resuscitation Council recommends that defibrillator paddle position is important as it influences flow of current through the myocardium.[2] The paddle positions recommended are: one electrode positioned below the outer half of the right clavicle and the other electrode positioned in the 5th intercostal space in the anterior axillary line. If repeated defibrillation is unsuccessful in this position, an alternative approach is to position one electrode to the left of the lower sternal border and the other posteriorly, just inferior to the scapula.[3] The latter position is also recommended in patients with implanted defibrillators or pacemakers. The polarity of the paddles does not matter as they are interchangeable.

In the case described, the patient was prone with pins screwed into the skull, covered with surgical drapes, and had an open surgical wound on the back of the chest. In addition, numerous intravascular lines and breathing circuitry connected her to the anaesthetic machine and monitors. Turning her into the supine position to carry out defibrillation and cardiopulmonary resuscitation would have taken several minutes. Movement of the now unstable column during this manoeuvre would almost certainly have resulted in spinal cord damage.

In neurosurgery, the prone position is commonly used for operations on the spine and occasionally for operations on the posterior fossa. In ICU, prone positioning is increasingly used to improve oxygenation in patients with acute respiratory distress syndrome. If such patients were to require defibrillation, the process of turning them supine to perform defibrillation would consume valuable minutes, which reduces the chances of successful defibrillation.

Catell *et al.* describe the use of electrical countershock in the prone position for the treatment of arrhythmias such as atrial fibrillation in ICU patients receiving prone ventilation.[4] They suggest that defibrillation should be carried out in the prone position as the first choice, if it is required in patients being nursed in the prone position. The case described demonstrates that defibrillation can be successful when performed in the prone position, and we believe it should be attempted if a defibrillator is at hand, and if turning the patient cannot be performed quickly.

The decision to continue with anaesthesia and surgery after the occurrence of runs of ventricular ectopics in the anaesthetic room was made on the basis that they did not have any haemodynamic ill effects, and that the surgery was palliative. However, with hindsight, it is probable that the early use of amiodarone could potentially have prevented the whole scenario.

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British Journal of Anaesthesia **87** **(6)**: 939–43 (2001)

Correspondence

Airway obstruction and microsleep after surgery

Editor—Rahman and colleagues[1] make the interesting observation that obstructed breathing in post-operative patients was more common when they were awake than when they were asleep. This seems to contradict our study[2] where we found obstructed breathing postoperatively only when patients were asleep.

There were important differences between the two studies. We[2] divided 32 patients into two equal groups, one having morphine, the other regional block. The dose of morphine was about 28 mg in 14 h and no opioid was used in the regional block group. In Rahman and colleagues' study three patients had a median dose of 51 mg morphine in the 14 h study period and five had thoracic epidural blocks which included opioids.

There are differences in the criteria of obstruction. Rahman and colleagues[1] defined obstruction as a phasic abdominal EMG pattern at *any time* or *any change* in nasal flow pattern during a 30 s measuring period. My reading of this is that one obstructed breath in a 30 s measuring period registered as a 30 s period of airway obstruction and if every breath was obstructed during the 30 s period it would give the same duration of obstruction. Our criteria and methods were different,[2,3] paradoxical breathing (partial obstruction) was where 50% of breaths in a 5 min period showed phase difference between the movement of ribs and abdomen and obstructive apnoea was recognized only when the sum of rib cage and abdominal movement contributing to tidal volume was zero for more than 10 s This means that Rahman and colleagues[1] would have detected many, very brief (< 10 s), periods of apnoea in 'awake' patients all of which we would have ignored. In our study, partial obstruction with snoring[3] lasting 5 or more min was the most common breathing pattern associated with hypoxaemia (Sa_{O_2} < 80%) but occurred only during sleep and only after morphine.

A further crucial difference is the assessment of the 'sleep/awake' state. While both studies used the same EEG criteria, Rahman and colleagues[1] defined patients as 'awake' up to EEG stage 2 whereas we defined a 'transition stage' of sleep at EEG stages between 1 and 2. Thus we labelled as 'asleep' some patients that Rahman and colleagues[1] would have labelled 'awake' using their criteria. Nevertheless, in this transitional group we found only 94 episodes of obstruction compared to 510 episodes when asleep. In Rahman's study, there were more episodes of obstruction in their 'awake' patients than when they were asleep. However, I propose that these brief periods of obstruction in patients whom Rahman and colleagues[1] define as 'awake', occurred in a non-steady state of altering consciousness or microsleep.

This raises the question about how we define sleep. Rahman and colleagues[1] remind us that the standard definition describes sleep as an EEG sleep pattern lasting more than half of the 30 s recording epoch Thus, loss of consciousness for a shorter period than 15 s cannot be defined as sleep using this criterion and therefore an obstructive episode during a period of unconsciousness for less than 15 s is registered as occurring during wakefulness. They are rightly critical of these 1968 EEG criteria devised for non-drugged sleep apnoea patients when applied to postoperative patients receiving opioids.

I suggest that these EEG criteria are inappropriate for detecting brief periods of loss of consciousness, which during sedation, are associated with the changes in muscle tone that are the recognized parts of the sleep phenomenon. Thus eye blink duration is a measure of sedation.[4] Normal blink duration is less than 500 ms (median 95 ms) but during sedation blink duration increased to more than 8 s. Inhibition of cortical processing of visual information precedes blink onset by 50 ms and persists for 200 ms after blink onset. In the context of driving a car at 70 mph (103 feet s^{-1}), a sleepy driver who blinks for 8 s will travel over 800 feet during which time the driver will have no conscious realization that the eye has closed. This brief loss of tone in the eyelid muscles reflects a loss of tone in the neck and elsewhere, probably including the upper airway, and represents microsleep, which is a feature of anaesthetic sedation.[4] I suggest that this may also be a common feature of opioid administration in the postoperative period, and that Rahman and colleagues[1] have identified transient airway obstruction during microsleep. While such brief periods of unconsciousness and hypotonia may be fatal in car drivers, they are probably harmless in postoperative patients in terms of worsening hypoxaemia.

Rahman and colleagues[1] extrapolate from the sleep apnoea syndrome to suggest that intermittent airway obstruction following opioids causes arousal and this disturbs sleep in postoperative patients. This might not be the case for the following reason. I was a subject in a study of the effects of morphine on breathing with and without a considerably increased airway resistance (80 cm H_2O litre^{-1} s).[5] I was surprised that morphine abolished the very unpleasant effects of this severe airway obstruction. Morphine predisposes to sleep, hypoxaemia and airway obstruction but part of its danger lies in reducing the arousal effects of the latter.

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Editor—Thank you for the opportunity to respond to Professor Jones' letter with his comments on our study. We agree that our findings contradict his study,[1] and that there are substantial differences in the methods used that make comparison of the two studies awkward. The most obvious of these is the use of very different time blocks, 5 min in his and 30 s in ours. We are also grateful for the opportunity to comment on some of the difficulties of studies of this type.

However, Professor Jones is wrong when he quotes our definition of airway obstruction. Our exact definition was: 'Respiration was considered abnormal if there was any change in the clear inspiratory and expiratory patten, or if the smooth

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domed appearance of the inspiratory wave was reduced in amplitude with a "flow limitation" pattern'. We considered each aspect of the records separately, for sleep, phasic activity, and obstruction, in identical 30 s epochs. In each of these 30 s epochs we applied the above criteria to the flow signal. Any period that contained an abnormality of respiration, was classified as abnormal. We do not believe that this resulted in too many periods being classified as abnormal We did not often observe the events he suggests, of brief periods of obstruction. Generally (although we have no exact data yet), the patterns we saw were either an abrupt change from small to large breaths or a persistent pattern such as we illustrate in our paper. We feel that this method of detection or obstructed breathing is not perfect but it does have considerable advantages over measurements of chest wall movements In our account, we cite our previous observations that the relationships between movement, flow, and effort are complex.[2] In particular, observations of oesophageal pressure and gastric pressure at the same time as chest wall movements suggest that in patients after abdominal surgery, chest wall movements are less reliable measures of obstructive apnoea, or even partial obstruction, than they may be in other circumstances. We were particularly keen to avoid bias, in association of events, by considering the signals separately. It is not clear if this was done in Jones' study.

We did not attempt to re-define sleep staging for our patients, although we were tempted! Jones is correct when he argues that there may be a 'transition stage'. In our study we stuck carefully to the criteria we cite. Patients were either awake, or asleep, which as we report was almost always stage 2. We did not consider stage 1 as awake, but we rarely saw this stage anyway.

Professor Jones' other observations are of interest, but we do not think, at present, that we have sufficient information to be certain what is going on when our patients have airway obstruction after surgery. We are presently gathering such data, which confirm that sleep disturbance and arousals are very prevalent, and also support the observations of the study we have just published, that such disturbances are not strongly linked to episodes of airway obstruction

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Anaphylactic reactions due to chlorhexidine allergy

Editor—We read with interest the case report by Stephens and colleagues.[1] We have had similar experience, with two life-threatening anaphylactic reactions occurring in the same patient who was also undergoing cardiac surgery and which we believe was due to chlorhexidine allergy.

A 71-year-old male was scheduled for elective mitral valve replacement for prolapse of the posterior leaflet of the mitral valve, causing severe mitral regurgitation. His past medical history included allergy to penicillin. Anaesthesia was induced uneventfully, using fentanyl, propofol, midazolam and pancuronium. During suturing of the right internal jugular central lines, the patient developed an acute anaphylactic reaction, characterized by urticaria, erythema and circulatory collapse. Bronchospasm was also not a feature in this case. The anaphylaxis was successfully managed with epinephrine, metaraminol, hydrocortisone and chlorpheniramine. Skin preparation for the insertion of neck lines had been with chlorhexidine. Surgery was abandoned and the patient was transferred to the intensive care unit where he made an uneventul recovery

Our patient was referred to a dermatologist who performed skin patch testing for midazolam, fentanyl, propofol, pancuronium and chlorhexidine. The only positive reaction was to chlorhexidine. We therefore postulated that the anaphylactic reaction could have been caused by the introduction of chlorhexidine to the circulation from the skin during insertion of the central line. The patient was rescheduled for surgery some weeks later, and preparation for anaesthesia included premedication with hydrocortisone, ranitidine and chlorpheniramine. Anaesthesia on this occasion was induced with etomidate, remifentanil, and pancuronium, again uneventfully. On this occasion, chlorhexidine was avoided in all skin preparations. However, once again following insertion of the central line, the patients developed an anaphylactic reaction in exactly the same manner as on the previous occasion. Resuscitation was successful using epinephrine, hydrocortisone and chlorpheniramine. The patient again made an uneventful recovery. The central venous catheters we used were not coated in any way with chlorhexidine. The serum tryptase was only moderately elevated.

We sought advice from a consultant immunologist and a consultant anaesthetist who run a specialist joint clinic to investigate anaphylactic reactions during anaesthesia. They tested for latex allergy, ethylene oxide allergy, and for the other drugs already mentioned, using skin prick testing. It was again considered most likely that the patient's reaction was due to the introduction of chlorhexidine in some way into the circulation. Surgery was rescheduled and on this occasion the patient was admitted to the intensive care unit the day before, where invasive monitoring was established avoiding chlorhexidine, under controlled conditions and without any adverse reactions. At this point, we considered other possible sources of chlorhexidine contamination. We realized that the anaphylactic reactions had occurred not only at the time of insertion of the central venous line, but were also temporally related to the insertion of the urethral catheter. In our institution, this is routinely performed by the surgical team, who use INSTILLAGEL® (Clinimed, High Wycombe, UK) to lubricate the urethra. On examination of the components of INSTILLAGEL®, we discovered that it contains chlorhexidine gluconate 0.25 g per 100 g. We believe that on each occasion the anaphylaxis was unrelated to the insertion of the central venous line and was caused by absorption of chlorhexidine from the urethral mucosa. Our patient was successfully anaesthetized and catheterized without the use of INSTILLAGEL® Anaphylaxis did not occur, and surgery and recovery were uncomplicated.

Review of the literature supports this theory, and we were able to find a number of case reports of anaphylaxis following absorption of chlorhexidine *via* the urethra.[2–4]

We were unaware that the urethral lubricant contained chlorhexidine and indeed, of the previously reported cases of anaphylaxis associated with urinary catheter lubricants. We advise caution with the use of chlorhexidine-containing compounds for urethral lubrication in any patient with a history of unexplained anaphylaxis, and emphasize the importance for anaesthetists to remain aware of 'non-anaesthetic'-related possiblilities for the introduction of potential allergens. We have since stopped using INSTILLAGEL® for urtheral lubrication.

A S Lockhart
C. C Harle
Blackpool
UK

1 Stephens R, Mythen M, Kallis P, et al. Two episodes of life-threatening anaphylaxis in the same patient to a chlorhexidine-sulphadiazine-coated venous catheter. *Br J Anaesth* 2001; **87**: 306–8

2 Wicki J, Deluze C, Cirafici L, et al. Anaphylactic shock induced by intraurethral use of chlorhexidine. *Allergy* 1999; **54**: 768–9

3 Mitchell D, Parker F. Anaphylaxis following urtheral catheterisation. *Br J Urol* 1993; **71**: 613

4 Russ B, Maddern P. Anaphylactic reaction to chlorhexidine in urinary catheter lubricant. *Anaesth Intensive Care* 1994; **22**: 611–12

Editor—We are grateful to Drs Lockhart and Harle for reporting their similar experience with chlorhexidine allergy and the opportunity to add some further comments.

We also had considered chlorhexidine in the skin preparation used for insertion of the urethral catheter, and the INSTILLAGEL® lubricant as potential causes of the anaphylaxis. Hence, we had also sought to avoid both of these agents on the second occasion. In fact, the anaphylactic episode occurred exactly as the urethral catheter had been placed on the first occasion, and it was the timing of this event that led us to believe that the urethral catheterization had been the likely precipitant!

However, on the second occasion, urethral catheterization had not yet occurred, as we were endeavouring to carry out each procedure separately as a precaution against confusing any subsequent adverse event, with a particular incident. On this occasion, the timing of the event coincided only with the i.v. flushing of the newly inserted central venous line. It was not appreciated at this time that this particular central venous line was coated in chlorhexidine. It was only subsequently when the package inserts were retrieved from the waste bins that the written warning to avoid such lines in patients with known sensitivity to chlorhexdine was appreciated.

We would, therefore, advise caution even when using equipment with which you are familiar, but in which there are identifiable package inserts which might not have been read for some time!

Wynne Davies
London
UK

Autologous transfusion in total knee replacement surgery

Editor—I read the recent study on autologous transfusion in total knee replacement surgery with interest.[1] We have recently introduced into our hospital postoperative drains, which allow re-transfusion of unwashed, filtered, autologous blood after knee replacement surgery (Bellovac A.B T., Astra Tech, Sweden). At approximately the same time, we introduced a transfusion 'trigger' of 9 g dl^{-1}. We audited the effectiveness of these drains and the 'trigger' in reducing the requirements for allogeneic transfusion compared to the previous year's transfusion data obtained from the hospital blood bank database. Twenty-four patients were audited and the results are shown in Table 1.

Both patients who received allogeneic transfusion had an Hb of 8.1 g dl^{-1} (i.e. below the 'trigger' and therefore appropriate). This represents an allogeneic transfusion rate of 8.3% of patients, compared to the historical data showing a transfusion rate of 25% (average number of units transfused 2.5, range 1–4). It is interesting to note that this is a similar reduction in allogeneic rate to that found in the study by Thomas and colleagues.[1]

Table 1 Effectiveness of postoperative drains and transfusion 'trigger' in reducing requirements for allogeneic transfusion

Volume reinfused (ml)	686 (200–1499)
Starting Hb (g dl^{-1})	13.9 (10.1–16.9)
Postoperative Hb (g dl^{-1})	11.2 (8.1–13.9)
Reduction in Hb (g dl^{-1})	2.76 (1.3–6.2)
Allogeneic transfusion	2 patients (2 and 3 units)

Table 2 Cost analysis comparing transfusion before and after new drains

	Before new drains	**After new drains**
Cost per patient of allogeneic blood per patients at current cost of £90 unit^{-1}	£54	£18.75
Cost of drains in excess of standard drains per patient	£0	£50
Total per patient	£54	£68.75

In the re-infused group there were two deep vein thromboses (DVT), one transient ischaemic attack, and one patient had a 'sweaty' episode during the autologous transfusion which was therefore stopped. The 'in-hospital' DVT rate of 8.3% compares favourably with quoted rates of 20% and 36%, which are at the lower end of the published range. A cost analysis is presented in Table 2. There was approximately £14 excess per patient after the introduction of the new drains, which is considerably better than the £113 excess per patient in Thomas' study.

One of the main worries about re-transfusion of unwashed blood is the possibility of the transfused blood containing an excessive amount of inflammatory mediators. Studies have shown that while this is the case, transfusion of this blood did not increase the circulating levels of these mediators.[4] In addition, it has been shown that infective episodes are significantly reduced by the avoidance of homologous blood.[5] I believe this audit suggests that the introduction of drain systems that allow re-transfusion of autologous blood, along with a transfusion trigger, can significantly reduce the amount of allogeneic blood used, and at the same time produce a cost saving without an excess of side effects.

J. C Hughes
Bridgend
UK

1 Thomas D, Wareham K, Cohen D, Hutchings H. Autologous blood transfusion in total knee replacement surgery. *Br J Anaesth* 2001; **86**: 669–73

2 Comp PC, Spiro TE, Friedman RJ, et al. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. Enoxaparin Clinical Trial Group. *Bone Joint Sur* 2001; **83**: 336–45

3 Blanchard J, Meuwly JY, Leyvraz PF, et al. Prevention of deep-vein thrombosis after total knee replacement. Randomised comparison between a low-molecular-weight heparin (nadroparin) and mechanical prophylaxis with a foot-pump system. *Bone Joint Sur* 1999; **81**: 654–9

4 Bengtson JP, Backman L, Stenqvist O, et al. Complement activation and reinfusion of wound drainage blood. *Anesthesiology* 1990; **73**: 376–80

5 Newman JH, Bowers M, Murphy J. The clinical advantages of autologous transfusion. A randomized, controlled study after knee replacement. *Bone Joint Sur* 1997; **79**: 630–2

Editor—I agree with the comments made by Dr J. C. Hughes. The use of re-infusion devices to return unwashed, filtered and salvaged blood has proved very successful following knee surgery. It is encouraging that, in his group of patients, he found a similar reduction in the use of allogeneic blood to our study, by employing a a transfusion trigger of 9 g dl^{-1} and using a blood salvage technique.

It appears that the re-infusion of relatively low volumes of unwashed blood following primary unilateral knee replacement surgery does not have serious clinical consequences. Larger volumes salvaged during other surgical procedures may cause greater clinical effects. Also, blood salvaged following hip arthroplasty may contain a greater concentration of inflammatory mediators.

The excess cost involved in postoperative salvage using a cell salvage machine as described in our paper was definitely overestimated. The operator time was calculated for the whole collection period and processing. In practice, this is not the case and the operators were able to carry out other duties whilst intermittently visiting the patient, to wash and process the collected blood.

We believe that with current costs, which now favour the use of any recycling equipment, providing one unit of blood is salvaged, almost all systems on the market are cost-effective. As we have a red cell salvage service in place with operating department personnel experienced in the operation of centrifugal devices, this is a standard of care we wish to continue. The use of simple re-infusion has, of course, been used with good results and may well suit the smaller orthopaedic units. Use of such devices for large volumes of recycled blood is unlikely to prove cost effective and may cause a greater inflammatory reaction.

D W. Thomas
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UK

Numbness a greater problem than pain?

Editor—In his article 'Analgesia for day-case surgery', Rawal[1] suggests that bupivacaine and ropivacaine are suitable solutions for brachial plexus blockade in patients having day-case surgery. These drugs last from 12 to 15 h[2] and most patients who have ever had a 'local anaesthetic' at the dentist will agree that the sensation of numbness and heaviness is extremely unpleasant.

Brachial plexus block performed using 1.5% lidocaine 35–40 ml with 1/100 000 epinephrine will produce analgesia lasting 3–6 h.[3] Most people having day-case surgery will be relieved when this block wears off. If patients are warned that their surgical site will be painful and, in anticipation of this, begin treatment with paracetamol or NSAIDs, I believe they would have greater satisfaction than if they were to return home to nurse a 'dead arm' for more than 12 h.

In my opinion, bupivacaine or ropivacaine should only be used to perform brachial plexus blocks on inpatients having extensive surgery and returning to a unit where there are experienced staff to help them cope with their numb limb.

Anthea Hatfield
Walsall
UK

1 Rawal N. Analgesia for day-case surgery. *Br J Anaesth* 2001; **87**: 73–87
2 Klein SM, Greengrass RA, Steele SM *et al* A comparison of 0.5% bupivicaine, 0.5% ropivicaine, and 0.75% ropivicaine for interscalene brachial plexus block *Anesth Analg* 1998; **87**: 1316–9
3 Bouaziz H, Kinirons P, Macalou D, *et al.* Sufentanil does not prolong the duration of analgesia in a mepivicaine brachial plexus block: a dose response study. *Anesth Analg* 2000; **90**: 383–7

Editor—Dr Hatfield recommends the use of lidocaine for brachial plexus block to avoid prolonged numbness at home, which she considers a greater problem than pain. My experience is the opposite; a well-informed patient is more likely to accept some numbness as a price for a pain-free extremity. I am not aware of any study which shows that patients perceive numbness as a greater problem than pain.

As indicated in the review article, the types of surgery under discussion are more complex than those performed by a dentist. Postoperative pain remains a significant problem for 30–40% of patients undergoing day-case surgery.[1] The treatment recommended by Hatfield (paracetamol) was ineffective in 42% of our patients undergoing hand surgery. In this controlled study, paracetamol, tramadol and dipyrone (metamizol) were compared for postoperative analgesia after hand surgery under brachial plexus block with 2% mepivacaine. Very few of the 120 patients included in the study complained of numbness at home, the most common complaints being inadequate analgesia, vomiting, dizziness and tiredness.[2]

Although numbness of the limb may be unpleasant, the patient should be allowed to participate in the decision-making based on information about the advantages and disadvantages of short- and long-acting local anaesthetic drugs. The information should also include the issue of numbness *vs* pain relief. It is well accepted that analgesia provided by local anaesthetics is superior to that provided by other alternatives, particularly for pain relief during physiotherapy-induced movement. This can be expected to result in a better surgical outcome. However, the superior analgesia of local anaesthetics comes at the cost of numbness. The problem can be reduced (but not eliminated) by the use of additives such as opioids and clonidine which may allow local anaesthetic dose reduction and provide prolonged analgesia. However, the current literature is inconclusive.[3] A better alternative would be to use a catheter technique and a disposable pump device which allows the patient to self-administer low-dose local anaesthetic at home.[4] Until such techniques become established, the decision regarding a trade-off between nursing a 'dead limb' or a very painful one should be made in cooperation with the patient. Let the patient decide!

Narinder Rawal
Örebro
Sweden

1 Rawal N. Analgesia for day-case surgery. *Br J Anaesth* 2001; **87**: 73–87
2 Rawal N, Allvin R, Amilon A, Ohlsson T, Hallen J Postoperative analgesia at home after ambulatory hand surgery—a controlled comparison between tramadol, metamizol and paracetamol. *Anesth Analg* 2001; **92**: 347–51
3 Murphy DB, Chan VWS. Upper extremity blocks for day surgery *Tech Reg Anesth Pain Mgmt* 2000; **4**. 19–29
4 Rawal N, Allvin R, Hallen J *et al* Ropivacaine versus bupivacaine for axillary plexus analgesia at home—a controlled trial of PCRA. *Int Monitor Reg Anaesth* 2000; **12**· 199

Ondansetron after Caesarian section

Editor—I was surprised to see a study in which onansetron had been given to mothers in the post-partum period,[1] since I am aware that manufacturers caution against its use in breast-feeding women. Were the women in the study made aware of the potential for unknown adverse effects on their baby? In my experience, women will tolerate far more serious symptoms than nausea if the heath of their baby depends on it. I am not belittling the distress casused by nausea, but I am concerned that it is unethical to subject women to a drug that may harm their baby. Thalidomide was also an antiemetic. The days of vague explanations and administration of potentially toxic drugs to uninformed patients should be consigned to the past.

Leyla Sanai
Glasgow
UK

1 Cherian VT, Smith I. Prophylactic ondansetron does not improve patient satisfaction in women used PCA after Caesarian section. *Br J Anaesth* 2001; **87**: 502–4

Editor—Thank you for allowing me to respond to this letter. The issue of breast feeding is always difficult, due to the lack of objective data for most drugs. A great many drugs are present in breast milk, although generally in small amounts. For the few that are not, the manufacturer is in the fortunate position of being able to declare their product safe while breast feeding. With the remaining drugs, either trace amounts are excreted in breast milk, or the fate of the drug is unknown. For obvious reasons, most pharmaceutical companies do not study the effect of maternally administered drug on breast-fed babies, choosing instead to simply issue a blanket caution. This is the current position for both ondansetron and prochlorperazine; there is no evidence that they are actually harmful, simply no proof that they are not. Thalidomide was altogether different, being given during the crucial period of organogenesis.

Despite the understandably cautious approach of the pharmaceutical industry, it is often necessary to administer drugs which are excreted in breast milk to lactating mothers. Both prochlorperazine and ondansetron are widely used in the postpartum period and, to date, there have been no reports or suggestions of any harm to newborn babies, despite their widespread use. Both drugs are routinely used in our institution (prochlorperazine as first line, ondansetron as rescue, for 'high-risk' patients or where the former is contraindicated). While we accept the need to warn all patients of potential risks, to do so in the absence of any evidence of such risk would be alarmist. It is therefore not our policy to warn breastfeeding mothers receiving antiemetics, and this policy was not altered during the conduct of the clinical trial.

We would be interested to hear what antiemetic is used in Dr Sanai's obstetric unit, since, in addition to ondansetron and prochlorperazine, the manufacturers caution against the use of cyclizine, domperidone, droperidol, granisetron, metoclopramide, promethazine and tropisetron during breast feeding. The choice of analgesic may be similarly problematic, since cautions also apply to morphine, pethidine, fentanyl, alfentanil, remifentanil, tramadol, several codeine preparations, and many NSAIDs.

Ian Smith
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Asystole during anaesthetic induction with remifentanil and sevoflurane

Editor—Severe bradycardia has been reported in patients receiving boluses of remifentanil.[1–4] Pre-existing cardiac disease, beta-blocking and calcium channel blocking drugs have been suggested as risk factors,[1,4] most of the cases being described in patients scheduled for fast track cardiac surgery.[1,2,5] The use of sevoflurane may also be a predisposing factor.[1] We report a case of asystole in a patient who was given remifentanil and sevoflurane for induction of anaesthesia. This 78-yr-old man was suffering from laryngeal cancer, and was scheduled for laryngeal endoscopy. He was a heavy smoker. He had been treated with 5-fluorouracil and cisplatin 1 month previously, but did not receive any medication at the time of anaesthesia. Pre-anaesthetic examination noted a basal heart rate of 62 beats min^{-1}.

In the operating theatre, after placement of an arterial pressure cuff, ECG, and pulse oximeter, the patient was preoxygenated with 100% oxygen. Anaesthesia was induced through a face mask with 8% sevoflurane in a mixture of 60% nitrous oxide and 32% oxygen. Loss of consciousness occurred after four vital capacity breaths and the patient was manually ventilated until the end-tidal sevoflurane concentration reached 5%. Mivacurium 0.2 mg kg^{-1} was given followed by an i.v. bolus of remifentanil 0.5 μg kg^{-1} over 1 min, and a 0.5 μg kg^{-1} h^{-1} continuous infusion. Within 1 min, heart rate decreased from 50 beats min^{-1} to asystole, unresponsive to i.v. atropine 1 mg. The remifentanil infusion was stopped immediately and 100% oxygen administered. Cardiac sinus rhythm resumed after two precordial thumps. The trachea was intubated and the laryngeal endoscopy was performed under 2% sevoflurane and a remifentanil 0.15 μg kg^{-1} h^{-1} infusion. No other episode of bradycardia or cardiac arrest occurred during anaesthesia or in the following 24 h of continuous heart rate monitoring. Postoperative ECG, plasma troponin concentrations and echocardiography were all normal.

Only one case of asystole has been previously reported in a patient given sevoflurane and remifentanil,[1] but several cases of severe bradycardia have been documented in patients receiving remifentanil.[1–4] In this case, where no other risk factor was documented, we postulate that the rapid sequence induction of anaesthesia with sevoflurane blunted sympathetic tone,[5] and allowed uncompensated parasympathetic activation by remifentanil. We thus recommend that induction of anaesthesia with sevoflurane should be avoided in patients about to receive remifentanil.

Okba Kurdi
Arnaud Deleuze
Emanuel Marret
Francis Bonnet
Paris
France

1 Wang JY, Winship SM, Thomas SD, Gin T, Russell GN. Induction of anaesthesia in patients with coronary artery disease. a comparison between sevoflurane-remifentanil and fentanyl-etomidate. *Anaesth Intensive Care* 1999; **27**: 363–8
2 Elliott P, O'Hare R, Bill KM, Phillips AS, Gibson FM, Mirakhur RK. Severe cardiovascular depression with remifentanil. *Anaes Analg* 2000; **91**: 58–61
3 Reid JE, Mirhakhur RK. Bradycardia after adminstration of remifentanil. *Br J Anaesth* 2000; **84**: 422–3
4 De Souza G, Lewis MC, TerRiet MF. Severe bradycardia after remifentanil. *Anesthesiology* 1997, **87**: 422–3
5 Ebert TJ, Harkin CP, Muzi M. Cardiovascular responses to sevoflurane a review. *Anaes Analg* 1995; **81**: S11–S22

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Book Reviews

CD Review: The Electronic Anesthesiology Library. 1996–2000. TEAL CD-ROM. Published by Lippincott, Williams and Wilkins, Philadelphia ISBN 1-800-638-3030.

This CD-ROM has the entire editorial content for the *British Journal of Anaesthesia, Anesthesiology, Anesthesia and Analgesia* and the *Canadian Journal of Anaesthesia* from 1996–2000. Installation was straightforward and clicking on the file *Setup.bat* installed the software automatically. If QuickTime is not installed on the computer, the system will install it automatically. The system could then be accessed without reading the instructions, which is a useful test for the ease of use of any software.

The database can be searched using three different techniques. The table of contents can be browsed by selecting a journal and then selecting an issue from a particular month. The result of double clicking on a *British Journal of Anaesthesia* monthly issue produces a list of the articles contained in that month's issue, but the list is hidden from immediate view and could be displayed better at this point. Double clicking on an individual article displays the full text version on the screen. The second method for searching is natural language free form entry. A natural language search is a simple technique to access the information required. Searches can also be performed by specifying one or more terms, such as authors or keywords, contained within the TEAL dictionary. However, the toggle to enable either a fuzzy logic or a Boolean search to be made is not very intuitive to find from the start screen, even using the printed instructions provided. There is no search facility in the help system for TEAL which is a disadvantage, but the system of quantifying the relevance of documents obtained in a search is extremely valuable. The filter can be adjusted for relevance to the search criteria or to emphasize the number of documents retrieved.

Clicking on a reference to an article which is contained on the CD-ROM displays the full text of that article. If the article is not contained in the TEAL database, an on-line link to a reference listed in the article launches a search into the Knowledge Finder web site when the computer is connected to the World Wide Web (www). This will link to the article if it had been published before 1996 and is therefore not contained in the CD-ROM. This is an impressive feature but does require connection to the www during the use of TEAL. Most anaesthetists and departments of anaesthetics in the UK will not have a continuous connection to the web and so, unlike in the USA, this feature may not be used widely. Tables and figures within the paper are viewed easily by clicking on the thumbnails presented at the side of the text. Figures and tables can also be copied into the clipboard and then pasted into a word processing document or slide presentation. The source of the item is retained when the item is copied which is an excellent feature.

A good test of any new technology is whether it is used with sufficient frequency to make its loss or return a major inconvenience. This CD-ROM qualifies as one I would not wish to return. While most of us have access to the www, it is extremely convenient to be able to view an article in its original form within a few seconds. However, the database cannot be used if the CD-ROM is not in place. The database can be loaded on to a hard disk but the software cannot access it there This will be a major disadvantage for many laptop users who may not travel with their CD-ROM in place to minimize weight. There are alternative methods of ensuring copy protection which do not reduce the convenience of use to this extent Most software systems can be improved but, overall, this is an extremely valuable package which should be available in all departments of anaesthesia.

Future technological developments will allow larger quantities of information to be stored on larger capacity disks and, hopefully, will also allow the TEAL database to be installed on a local disk drive to avoid having to transport a separate drive unit. As more anaesthetists incorporate hand-held computers into their daily practice, we will inevitably see software such as this electronic library being made available for these truly portable systems.

Gavin N. C. Kenny
Glasgow

Low Flow Anaesthesia. The Theory and Practice of Low Flow, Minimal Flow and Closed System Anaesthesia. 2nd English Edn. Jan A. Baum. Published by Butterworth-Heinemann. Price £45. ISBN 0750646721.

This is the second English edition of a German textbook, the first being published in 1996. The book has been translated into Chinese as well as Italian and Korean. This English edition is a third larger than its predecessor and has about 500 references, most of them to recent research.

The reviewer of a book of this sort has a difficult task The reader requires some outline of what is in the book, how well and completely the subject is covered, how up-to-date it is, and how it compares with other works on the same subject There is no room for much criticism of detail but there must be some, if only to show that the reviewer has in fact read the book. An attempt is made below to comply with these requirements.

There is increasing interest in the subject of inhalational anaesthesia using low rates of fresh gas flow. The reasons for this interest are not hard to discover. The lower the fresh gas flow, the less do anaesthetic agents pollute the environment. Very considerable reductions in the cost of expensive agents can be made. Low flow systems are favourable to various forms of feedback and electronic control. These features are expounded and documented comprehensively in this book.

The advantages are so great that is appears surprising that low flow methods have been so relatively neglected. One major reason is exemplified by the report here of how Dr Francis Foldes attempted to report a series of more than 10 000 cases successfully anaesthetized using a fresh gas flow 1 litre min^{-1}. No American anaesthesia journal would accept the paper as it was considered that the technique carried a risk of hypoxia! When a high fresh gas flow is used, the composition of the gas mixture breathed by the patient is known and set up by the anaesthetist. The lower the fresh gas flow, the more the composition of the gas in the system deviates from that of the fresh gas and, until recently, this could be unknown to the anaesthetist. Now, with the routine use of oxygen and agent monitors, this serious objection to the use of low flow and closed systems is removed.

The deviation of the composition of the gas in the system (breathed by the patient) from that of the fresh gas is caused by interaction between the patients and the delivery of agent by the system. This is a feature absent from high flow systems. The explanations of these deviations is often complex and at this point a defect has to be mentioned. The book is translated from the German and it is in complex explanations that this becomes most obvious, sometimes to the point of obscurity. Againt this, particularly in the section on control, use is made of computer simulations of changes in agent concentrations in systems

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resulting from changes in fresh gas flows and other variables. These summarize complex changes with clarity Programs of the sort described must play an increasing part in educating anaesthetists in the future. Returning briefly to the complaint about language, the word 'technical' is greatly overused. It could be expunged from the whole book without any change in meaning of the sentences in which it is placed.

The first chapter deals with the classification of breathing systems This is often a difficult area. A large part of the problem is that the function of these systems depends not only on the arrangement of the components but also on the magnitude of the fresh gas flow and of the type of ventilation, whether spontaneous or controlled. The 'Mapleson Systems' are categorized as flow controlled non-rebreathing systems The idea of partial rebreathing with no carbon dioxide retention, although mentioned, receives no emphasis. The function of reservoir bags to cope with peak respiratory flow rates is nowhere mentioned. In connection with the Mapleson A (Magill) system, it is stated that if the reservoir volume is 'comparatively small', air may be drawn into the system This is not normally the case. An unhelpful distinction is made between semi-open and semi-closed systems. This chapter cannot be recommended to the examination candidate.

The following chapter on the history of rebreathing systems is of interest and gives references and illustrations which support claims that the first circle system with valves and soda lime was developed and used in Germany in 1924. This precedes the Sword (1930) reference usually given by Anglo-American authorities on the history of the circle system.

The following chapter on the pharmokinetics of anaesthetic gases is also of interest. The work of Harry Lowe (Lowe and Ernst, 1981) is largely followed. Oxygen uptake is estimated using Brody's Law which relates O_2 uptake to the body weight raised to the power of 0.75 ($kg^{3/4}$). This gives a figure of 242 ml for the 70 kg subject, a figure which is high for the anaesthetized patient. Examination of the zoological literature reveals that Brody's Law is a correlation across the animal kingdom and that within a species the correlation of oxygen uptake with body weight is given more accurately by kg to the power of 0 66. This quibble is only of significance in strictly closed systems.

The next few chapters discuss most aspects of the practice of low flow anaesthesia. Four techniques are distinguished, Low Flow (Foldes, 1952) having a fresh gas flow (FGF) of 1 litre min^{-1}, Minimal Flow (Virtue, 1974) having a FGF of 0 5 litre min^{-1} and two modes of closed system operation. In the first of these modes, the FGF is reduced to the gas uptake of the patient and this is termed a 'Non-quantitative Closed System' In the second mode, the composition of the gas in the system is kept constant by electronically controlled feedback loops and this is termed 'Quantitative Closed System'. The distinction between these two modes is a valid one; full gas monitoring (agent and oxygen) is necessary in both modes but only a feedback loop, using the end-expired agent concentration to precisely control the injection of agent into the system, can maintain a constant concentration. Manual control is inevitably bumpy. A number of experimental machines using this principle have been made and used successfully, but the Draeger Physioflex is the first to be commercially available.

A feature of low flow anaesthesia is the difficulty of getting enough anaesthetic into the patient during induction and this subject is fully discussed. Two methods of dealing with this problem are direct injection of liquid agent and the use of vaporizers of the Goldman type mounted in the circle. Given agent monitoring, both methods give good results with minimal equipment but the author regards both with disfavour, as obsolete and for use only by enthusiasts. For the 'western world' he is probably right but it is useful to have some references to their use

Much of the book is taken up with a detailed examination of the suitability or otherwise of much anaesthetic equipment of use with low flow techniques and this must be of value to the practising anaesthetist.

Other subjects covered include the accumulation of other gases in closed systems (nitrogen, carbon monoxide, methane, hydrogen, etc.) Improvements in soda lime are discussed It is noted that many of the safety measures now being put into place to control oxygen may prevent the use of low flow techniques The safety aspects of the slowness of change of gas concentrations in low flow systems is emphasized under the heading of 'The Long Time Constant'. Isoflurane is considered to be the most suitable of the group of older anaesthetic agents to be used in low flow systems. In the author's department, no COHb has been detected after low flow anaesthetics using desflurane but care must be taken that no desiccated soda lime is used It is agreed that low flow anaesthesia is not feasible for anaesthetics of less than about 15 min duration.

The final 'Future Perspectives' chapter is of course most interesting Nitrous oxide having been given the thumbs down, oxygen as the sole 'carrier gas' is considered. Two very recent references are given to support the view that the use of 100% oxygen over a period of 12 h does not impair pulmonary function Finally, the use of xenon for clinical anaesthesia is considered This is particularly relevant because the great cost of this rare gas (concentration in air 0.086 ppm) necessitates the use of a closed system. The subject receives a good, fully referenced review

To summarize, this is a comprehensive text book on low flow anaesthesia, well referenced with references dating up to the year 2000. It is stronger on practical matters than theoretical ones but that will not lessen its appeal to most anaesthetists. There are no other recent textbooks devoted entirely to this subject The use of low flow anaesthesia must be encouraged and this book should be in every anaesthesia department library. The Association for Low Flow Anaesthesia (ALFA) meets annually and its meetings are widely advertised.

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More Case Presentations in Paediatric Anaesthesia and Intensive Care. Neil S. Morton, Edward I. Doyle, Jane Peutrell, Ros Lawson and Pam Cupples. Published by Butterworth-Heinemann, Oxford. Pp 161, indexed; illustrated. Price £14.99. ISBN 0750642157.

This volume complements the previous set of case presentations in paediatric anaesthesia and intensive care published by Drs Morton and Doyle in 1994. The format is similar, with a clinical scenario presented at the beginnig of each chapter. followed by three or four pertinent questions Answers are then given to the questions, with a summary of the main learning points and some key references at the end of each chapter

Thirty-two paediatric clinical problems are featured in this volume, varying from the relatively common (laryngospasm during induction, neonatal resuscitation), to the esoteric (problems in children after lung transplantation, epidermolysis bullosa). There is little overlap with the previous volume, with the exception of Pierre Robin Syndrome The discussion on difficult intubation has been expanded, with more detail on fibreoptic technique in babies. The two volumes effectively form a larger book, with 76 scenarios in total. Most of the advice from 1994 remains sound.

The intensive care emphasis is perhaps less in this volume than previously. Few of the cases would present primarily to the paediatric intensive care unit (PICU), for example, new techniques of extra-corporeal life support, SVT in a baby. However, a number of other cases would usually be managed postoperatively on the PICU or neonatal intensive care unit (NICU), for example, gastroschisis, congenital lung cyst, necrotizing enterocolitis, oesophageal atresia. As the authors state in their preface, paediatric intensive care is evolving into a specialty in its own right.

The preface also mentions specialists who occasionally look after children. Some of the scenarios would be relevant here· consent; asthma; suturing a laceration in A and E; day-case anaesthesia; pain management in medical patients; dental treatment in Trisomy 21; and children with learning difficulties. However, these days, most of the cases would probably fall into the domain of the specialist paediatric institution. Indeed, some of these problems would be rarely encountered by an individual anaesthetist in a regional paediatric centre!

The meat of the book is in the answer section of the chapters. Given the space constraints of a slim volume, the advice is generally accurate and well considered. Some sections could be usefully expanded a little. For example, in the chapter on tracheo-oesophageal fistula, the value of the neonatal bronchoscope in seeing the tracheal site of the fistula and identifying the rare double fistula, prior to repair, is not mentioned. Perhaps the authors might consider putting the cases on a web site and inviting discussion.

Most anaesthetic departments and PICUs should buy the book and it will be particularly valuable as a learning resource for SpRs. Consultants will find many of the scenarios useful and some challenging. I congratulate the authors for producing another inexpensive and compact compendium of problems, reflecting current paediatric anaesthetic practice.

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Resuscitation in Pregnancy: A Practical Approach. Philip Jevon and Margaret Raby. Published by Butterworth-Heinemann, Oxford. Pp 122; indexed; illustrated. Price £14.99. ISBN 0750644575.

This is a slim, pocket-sized book with an abstract cover. One author is a resuscitation training officer, and the other a midwife. An anaesthetist and an obstetrician are listed as consultant editors, so this is truly a multidisciplinary book. The foreword from the midwife assessor for the Confidential Enquiries makes it clear that the book is intended for midwives, and the preface from the authors stresses the importance of preventing aortocaval compression and the place of perimortem Caesarean section.

The book begins with a synopsis of the Confidential Enquiries, and then summarizes the physiology of pregnancy. It provides a plan for the layout of a resuscitation trolley and then launches into a series of chapters that are similar in content to the resuscitation manuals that accompany the Resuscitation Council's courses. Basic and advanced life support, with a suitable obstetric slant, and an algorithm for anaphylaxis, follow All this is done in an easy reading style with an abundance of bullet points, illustrations and references. Finally, the book deals with a description of the paperwork required for reporting a maternal death, and provides addresses for the amniotic fluid embolus register and the available life support course providers. There is also a chapter on training. We used the information provided in the chapter on ethical and legal issues to write a guideline for 'Do Not Resuscitate' orders.

Since the *British Journal of Anaethesia* is probably not read by midwives, you might wonder why we should review it. Anyone who is involved in teaching midwives will find this small book an extremely useful resource. Some of the information, I hope I shall never need. If pressed, I could find one or two points to criticize. The place of perimortem Caesarean section is emphasized in the preface and then rather gets lost in the rest of the book; but then I am a doctor, and the book is intended for midwives. The human wedge would have been better illustrated than described, but I am reluctant to be negative about something that is so clear and readable, and extensive. The way the book covers the issues around and beyond resuscitation was an unexpected bonus that will appeal to medical staff with a responsibility for the service. The more I delved into this book, the more impressed I became. At less than £15, it is a bargain that you can afford to present to your delivery suite.

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Intensive Care in New Zealand. A History of the New Zealand Region of ANZICS. R. V. Trubuhovich and J. A. Judson. Published by R. V. Trubuhovich and J. A. Judson. Pp. 150; illustrated. ISBN 0473076195.

The place of anaesthetists in the intensive care unit became established during the polio epidemics of the late 1940s and early 1950s. The rapid development of intensive care medicine is fascinating, all the more so because many of the early pioneers are still accessible, and their 'recollections are fresh and reliable'. The authors of this book, current and retired practitioners of intensive care in Auckland Hospital, have painstakingly researched and recorded the history of intensive care in New Zealand up to the year 2000, in a small volume of some 150 pages.

The book begins with a brief history of the introduction of IPPV on general wards, and thus a shift in the management of the critically ill (usually as a result of croup, tetanus and polio) from infectious disease specialists to anaesthetists. The impetus for the development of intensive care medicine in New Zealand (and, indeed, worldwide) originated with a Scottish anaesthetist, Matt Spence, who worked in Auckland between 1952 and 1983. He died in 1994, and such was the esteem in which he was held, that six pages of this book are taken in tributes to him.

The authors were among the founding members of the Australia and New Zealand Intensive Care Society (ANZICS), which was established in the mid 1970s. The setting up of this and other organizations (and the squabbling over the currency in which fees might be paid!) is described. A year-by-year account of the minutes of the AGMs, newsletters, and conferences from the New Zealand region of ANZICS is documented in some detail. There then follows a brief biography of office bearers of this region. It is heartening, though not surprising in this land of great beauty, to read that the energy of many of these people is directed not only at their profession but also to their many and varied outdoor sports, which include skiing, windsurfing, fishing and flying!

The history of each of New Zealand's 32 intensive care units is then summarized, and the book ends with a section on current issues in intensive care units in New Zealand, such as staffing, standards, centralization, education, research, etc.

This book is a well-researched, comprehensive and factual account of intensive care in New Zealand Although it is an archive, its style is fairly chatty, and it is therefore not as dry to read as one might imagine. It is probably of limited interest to those who have not worked in New Zealand, and in recognition of this, printing has been limited to 1000 copies. Nevertheless, it should be an inspiration to anyone else wishing to document the development of intensive care medicine in their own region, before this information is lost in the mists of time.

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British Journal of Anaesthesia **87** (6): 947 (2001)

Erratum

*Downward movement of syringe pumps reduces syringe output (BJA 2001; **86:** 828–31)*

The authors would like to correct p. 830, second paragraph in our article. A conversion error occurred while transforming the infusion rate of the syringe pumps for the compliance measurements from ml h^{-1} into µl s^{-1}. The reported compliances therefore have to be divided by 60.

'Testing the compliance of the different systems resulted in **identical** values for the Injectomat-C and the Perfusor fm **of 1.4** µl mm Hg^{-1}. The compliance of the IVAC 770 system was greater, at **1.7** µl mm Hg^{-1}. There was a statistically significant positive correlation (r^2=0.863, P<0.05) between time without infusion and the compliance of the system.'

This correlation has been retested and remained unchanged as suspected.

The authors apologize for this conversion error.

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The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

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Investigations, and Short Communications) but not for Reviews, Case Reports, or Commentaries. It should give a a succinct account of the problem, in up to 250 words. It may be used as it stands by abstracting journals. References are not used in this section, except in exceptional circumstances.

Three to five key words or phrases (for indexing) should be included below the summary.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the international non-proprietary name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

Description of results, while concise, should permit repetition of the investigation by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. Significance should be given as values of probability.

Discussion

The discussion should not merely recapitulate the results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially. Individuals named must be given the opportunity to read the paper and approve their inclusion in the acknowledgements, before the paper is submitted.

References

There should be a list of references at the conclusion of the paper, commencing on a new sheet.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically.

References in text, tables and legend should be identified by arabic numbers appearing in the text in superscript, for example ^{5} or $^{5-7}$ or ^{5}<space>^{16} for unrelated references. When a table, figure is first mentioned, its reference must continue the sequence.

Use the style of references adopted by the US National Library of Medicine and used in *Index Medicus.* The titles of journals should be abbreviated.

The names and initials of more than six authors should be abbreviated to three authors followed by *et al.*

Text references to 'unpublished observations' or 'personal communications' should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted and accepted for publication should be included in the list, the phrase 'in press' replacing volume and page number. Information from manuscripts submitted but not yet accepted should be cited in the test as unpublished observations.

Examples of correct forms of references:

Journals:

1. Brown BR jr, Gandolphi AJ. Adverse effects of volatile anaesthetics. *Br J Anaesth* 1987; **59**: 14-23

Chapter in a book:

2. Hull CJ Opioid infusions for the management of postoperative pain. In. Smith G, Covino BG, eds. *Acute Pain.* London: Butterworths, 1985, 155-79

Monographs:

3. Moore, DC. *Regional Block*, 4th Edn Springfield, Illinois· Charles C Thomas, 1979

Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in *Index Medicus* journals.

It is essential that authors verify the content and detail of references which they list against the original articles, as this responsibility cannot be accepted by either Editors or publishers.

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All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with Arabic numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used. Footnotes are not used.

Illustrations

Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not

be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black indict ink on white paper and, if in sets, should be presented at a uniform magnification. Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text, and using Arabic numbers. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the figure (and not in the legend) should be chosen from the following available types:

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The names of the author and title of the paper should also be written in soft pencil on the back of the illustrations.

It should be noted that A4-size figures generated by computer are usually unacceptable (see Extended Guide to Contributors—*Br J Anaesth* 2000; **84**: 131-7).

General information

Instructions to the printer Words to be printed in lowercase italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

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A **Results (bold)**
B *Lung function studies* (italics, ranged left)
C *Volume.* Large volumes . . . (italics, ranged left, text run on)

Symbols and abbreviations. In accordance with Editorial adoption of SI units, abbreviations and symbols should follow the conventions described in the booklet *Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors* (D. N. Baron, ed.) (1988), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with 'z' rather than 's' spelling in, e.g. organize, organization.

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Authors are encouraged to submit short manuscripts suitable for rapid publication. In general, these should conform to the requirements outlined above, but with the following differences.

Format. Summary; Introduction (not headed); Methods and results; Comment.

Size. Not more than 6 references, 1 table or 1 figure, one-and-a-half pages of printed text (1200 words)

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Each issue of the journal will contain correspondence. Correspondence arising from papers in a recent issue is published without delay, and for this reason, will be given priority over that pertaining to original research. The Editor may change, delete or modify in any way all items of correspondence.

All communications designed for publication should be submitted on a separate page in letter quality heavy type (not dot matrix), double-spaced, on one side only of the paper, with a wide margin. Contributors should send three copies of all correspondence to the editor and retain a copy in case of loss. Correspondence may also be submitted on disk. All authors must sign the accompanying submission letter.

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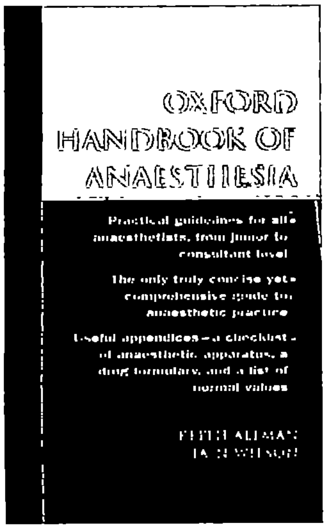
Corresponding authors will receive a copy of the journal in which their article appears. Offprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

IMPORTANT NOTICE TO AUTHORS

Structured Abstracts. From January 2002, the Summary of all Clinical Investigations, Laboratory Investigations and Short Communications (but not Reviews, Case Reports or Commentaries) published in the *British Journal of Anaesthesia* will be structured under the headings: Background; Methods; Results; Conclusions



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